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HEART BLOCK IN ADULT PATIENTS IN HOSPITAL PRACTICE*

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FROM mid-1949 through 1956, 25,000 routine electrocardiograms (ECG) were taken on 12,304 patients on the public wards of the Toronto General Hospital. The majority of the records consisted of 6-lead tracings, e.g. standard limb leads and V_1, V_3, and V_5 chest leads. Further chest leads and unipolar limb leads were frequently recorded, and towards the end of this period the usual 12 leads were adopted as routine. These ECG records have been reviewed and classified into various patterns (Table I).

TABLE I.—SUMMARY OF 25,000 ECG RECORDS ON 12,304 PATIENTS (1949-56)

	No.	*%*
Normal ECG	5389	43.8
Arrhythmia	2028	16.3
Cardiac infarction	2192	17.6
Left ventricular hypertrophy	1080	8.8
Right ventricular hypertrophy	284	2.3
Left bundle branch block	387	3.1
Right bundle branch block	367	3.0
Miscellaneous	250	(approx.)

The incidence of the various ECG patterns encountered in the records from which the 349 cases of heart block in this series were obtained.

Detailed study of the 349 cases of prolonged AV conduction (heart block) was undertaken. In nearly all cases the PR interval apparent in lead 2 was 0.02-0.04 second longer than in most other leads, particularly lead V_1. At times, however, the PR intervals in lead 2 and lead V_1 were identical, and rarely that in V_1 was 0.02 second longer than in lead 2.

In some examples of wide, split "P mitrale" the impression was gained that the PR interval was increased to, or just beyond, the upper limit of normal by a wide P wave of 0.12 second's duration. Inaccuracy in measurement of PR interval may also result from uneven action of the camera in association with fixed time markings on the graph.

The PR interval in normal individuals has been shown to be as long as 0.22 second in lead 2.[1, 2] In large series of healthy young men reported from the military services by Hall, Stewart and Manning,[3] by Graybiel *et al.*[4] and by Ferguson and O'Connell,[5] between 1 and 2% showed PR intervals over 0.20 second and in almost 0.5% cases the PR interval was 0.24 second or more, the longest being 0.36 second.

INCIDENCE

Heart block was present in 2.8% of those having electrocardiographic examination (Table II). Of the 6915 cases showing abnormality in one or more ECG records, heart block occurred in 5.0%.

Of the 349 cases of heart block, prolongation of PR interval beyond 0.20 second was found in 255 (73%); incomplete (second-degree) heart block in 73 (21%); complete block (third-degree) in 95 (27%). There was considerable overlapping among the various categories of heart block: 35 cases (10%) showed both first- and second-degree heart block; 29 cases (8%) showed both first- and third-degree heart block; 20 cases (6%) showed second- and third-degree block; and 11 cases (3%) showed all three degrees of block at different times.

TABLE II.—SUMMARY OF THE ARRHYTHMIAS IN 25,000 ECG RECORDS ON 12,304 PATIENTS (1949 - 56)

	No.	*%*
Total arrhythmias	*2028*	*16.3*
Atrial fibrillation	1251	
Atrial flutter	130	
Atrial tachycardia (no block)	41	
Paroxysmal auricular tachycardia with block	109	
A-V nodal rhythm	61	
Ventricular tachycardia	27	
Ventricular fibrillation	4	
Bigeminal A.P.B's	6	
Bigeminal V.P.B's	50	
Heart block	*349*	*2.8*
(1) Prolonged PR	255	2.0
(2) Incomplete heart block	73	0.6
(3) Complete heart block	95	0.8

The frequency of the significant arrhythmias encountered in the ECG records of 12,304 patients is shown. Heart block forms 17.2% of the arrhythmias.

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FINDINGS IN FIRST-DEGREE HEART BLOCK

In series of hospital patients Campbell[6] reported that 2.2% of cases showed prolongation of the PR interval. White[7] stated the incidence of this abnormality to be 3%. The present series shows 2.0% of cases with this finding in one or more ECG records.

Segregating cases showing first-degree block only, Logue and Hanson[8] found that as many as 34% presented no plausible explanation for the block. This figure will vary depending on the source of the cases studied. In the present series 12 cases (3.4%) showed no evidence of heart disease.

FINDINGS IN SECOND-DEGREE BLOCK

The length of the PR interval in the last conducted beat before a missed beat in incomplete block has been an intriguing study. When the block was 2:1, the PR intervals of the conducted beats were about equally distributed between those of normal duration, moderate lengthening (0.21-0.30 second), and marked lengthening (0.30 second). But when the Wenckebach phenomenon was present, or when there was only a very occasional non-conducted beat, the PR interval of the last conducted beat was never normal and there were twice as many over 0.30 second as between 0.21 and 0.30 second (Table III). No example of "reverse" Wenckebach phenomenon was encountered.[9]

TABLE III.—INCOMPLETE HEART BLOCK—73 CASES
LAST PR INTERVAL BEFORE A MISSED BEAT

	2:1 block	*Wenckebach*
PR normal	8	0
PR 0.21 - 0.30 second	10	17
PR over 0.30 second	5	33

The obvious difference in average AV conduction time of the last conducted beat is shown for the two types of incomplete or second-degree block.

Much is reported in the British literature of the difference between two types of partial or incomplete heart block. Gilchrist[10] labels type I the progressive lengthening of successive PR intervals leading to single missed beats (Wenckebach phenomenon), whereas type II shows abrupt rhythmic omission of ventricular beats in regular sequence without lengthening of the PR interval. Campbell[7] attempts to explain the latter on the basis of alteration in the excitability of the myocardium as well as in conductivity.

The present series confirms the findings of these investigators that the last PR before the missed beat was much longer on the average when the Wenckebach phenomenon was present than the PR of the conducted beat of a 2:1 block. However, when the eight cases showing a normal PR of the conducted beat during 2:1 block were studied, it was found that, in each case, either or both first- and third-degree block was present in the same case at other times. This suggests that impaired conduction was the more likely fundamental disturbance.

FINDINGS IN THIRD-DEGREE BLOCK

In complete AV dissociation, atrial activity was usually normal (86 of 95 cases). Slow irregular sinus activity occurred in two cases, while a fast sinus or atrial rate was seen in five. Atrial fibrillation and/or standstill was present in six cases; three exhibited atrial flutter temporarily.

The ventricular rate in complete block was relatively constant in the same case from day to day. The majority (82 of 95 cases) had a ventricular rate between 30 and 60/minute. Five cases showed a rate slower than 30/minute, the slowest being 22/minute. One case showed simply a temporary cessation of conduction without any idioventricular beats.

TABLE IV.—COMPLETE HEART BLOCK—95 CASES

Atrial rate or rhythm		*Ventricular rate*		*QRS*	
Slow	2	Under 30	5	Narrow	40
Normal	86	30 - 60	82	LBBB	23
Rapid	5	Over 60	10	RBBB	24
Fibrillation	6	Faster than atrial	5	Wide (varying)	1
Flutter	3	Gaps only	1		

The ECG findings of interest encountered in the 95 cases with complete AV dissociation.

In 10 cases the ventricular rate was over 60/minute, the fastest being 125/minute. In five of these 10 cases the ventricular rate exceeded the atrial rate. In cases of transient complete heart block the ventricular rate tended to be more rapid than in those with established complete block. When complete block had become established in later life, the ventricular rate was usually slower and exhibited less variation in rate from day to day.

The incidence of complete heart block in this series was 0.8% (95 cases in 12,304 patients) (Table IV); this agrees remarkably well with the 0.6% reported from Guy's Hospital by Campbell[11] and 0.8% in 10,000 cases by White.[7]

Of the 95 cases with complete heart block in this series, 49 (52%) had other grades of block at other times. Campbell[11] reports that 50% of his 64 cases showed varying degrees of block. Gilchrist[10] found 46 cases of chronic established complete heart block amongst 148 cases of "high-grade block", which by inference indicates that 67% showed varying block.

When the 47 cases in which complete heart block was the only rhythm recorded were segregated, the prognosis was found to be poor. Twenty-seven patients in this group died (57%) and 19 of these 27 had fresh myocardial infarction.

Stokes-Adams attacks occurred in 26 of the 95 patients with complete block. Of these 26, 11 died, a 42% mortality.

Age distribution of the 349 cases is shown in Fig. 1. The sharp rise in incidence of heart block of all grades after middle life is apparent. The factors responsible for this finding were the frequency of congestive heart failure and cardiac in-

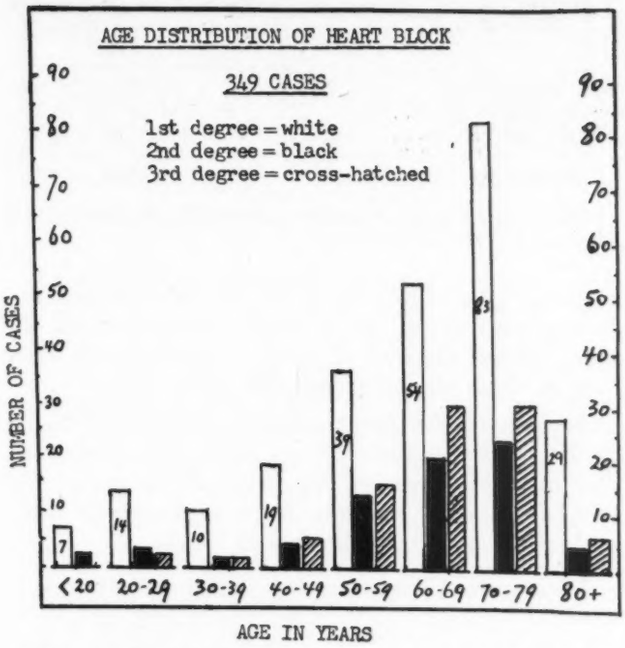

Fig. 1.—Shows an early peak in the third decade, but the main incidence is found in later life.

farction in this age group in association with their increased sensitivity to digitalis. In addition there is a minor early peak in the second or third decade, due probably to the influence of acute rheumatic fever in this age group.

As expected, the commonest form of heart disease was that due to arteriosclerosis, which was present in 154 cases. Cardiac infarction was present in at least 115 cases. Aortic stenosis was present in 37 cases, and possibly in another 10. Aortic insufficiency was present with stenosis in 7, and without stenosis in 12 cases. Hypertension was the etiological cause of the heart disease in 25 cases; congenital septal defects or pulmonary stenosis in 10. Acute rheumatic fever was present in 14 cases and rheumatic heart disease in 29 cases, largely manifested in the form of mitral stenosis. Less common diagnoses included subacute bacterial endocarditis in six cases, thyrotoxicosis in seven, myotonia atrophica in four, myxedema in two, cor pulmonale in one, Marie-Strümpell spondylitis in one, toxic myocarditis in one, and paroxysmal atrial tachycardia with congestive failure in one. No heart disease could be diagnosed in 10 cases, while paroxysmal atrial fibrillation occurred in three, vagal effect in one, and anxiety neurosis in one.

Congestive heart failure was present in 115 (33%) of the 349 cases of heart block (Table V).

TABLE V.—CONGESTIVE HEART FAILURE

	Cases	*Total*	*%*
First-degree block	93	255	36
Second-degree block	20	73	27
Third-degree block	18	95	19
Whole series	115	349	33

Congestive failure was less likely to be present as the heart block increased.

TABLE VI.—STOKES-ADAMS ATTACKS IN:

	Cases	*Total*	*%*
First-degree block	10	255	4
Second-degree block	11	73	15
Third-degree block	26	95	27
Whole series	34	349	10

The incidence of Stokes-Adams attacks increases with the severity of the heart block.

It was found more frequently in first- than in third-degree block and roughly parallels the influence of digitalis administration in causing the conduction defect (see Table XI).

Diabetes mellitus was recorded in 39 cases (11.2%).

Stokes-Adams attacks occurred in 34 (10%) of the 349 cases (Table VI). As was expected, the incidence of Stokes-Adams attacks increased with the severity of the heart block (Table VI).

TABLE VII.—DEATH IN HOSPITAL OCCURRED IN:

	Cases		*Total*	*%*
		Autopsies		
First-degree block	63	40	255	25
Second-degree block	21	6	73	29
Third-degree block	38	21	95	40
Whole series	103	(57)	349	30

Mortality increases with the severity of the heart block.

Death occurred in hospital in 30% of the patients in the entire series. Further details are provided in Tables VII and VIII. The mortality increases with the severity of the heart block. However, there is a high mortality (25%) among patients with first-degree block which is related to the frequency of congestive heart failure and digitalis administration in the elderly.

TABLE VIII.—MORTALITY IN SUBGROUPS

	Cases	*Total*	*%*
First- and second-degree block (only)	4	24	17
First- and third-degree block (only)	7	19	38
Second- and third-degree block (only)	2	11	18
All three degrees of block	3	11	28

The cases of varying degrees of heart block show no definite trend, but the numbers are small.

Details of the 11 cases showing all three degrees of block are recorded in Table IX. Their numbers

TABLE IX.—ALL THREE DEGREES OF HEART BLOCK 11 OF 349 CASES (3%)

Age range: 23 to 78		
Etiology:	Infarction	5
	Aortic valve disease	2
	Digitalis	2
	Arteriosclerotic heart disease ± digitalis	1
	Toxic myocarditis	1
Stokes-Adams attacks		4

TABLE X.—96 CASES OF RECENT CARDIAC INFARCTION WITH HEART BLOCK

Age	75 patients over 60 (78%)		
Sex	46 females (48%)		
Digitalis	A factor in 29 cases, likely cause in 14		
		Cases	*Mortality*
Site of infarction			
Anterior		31	17 (55%)
Posterior		51	19 (37%)
Septal		14	4 (35%)
Degree of block			
First		51	18 (35%)
Second		28	9 (31%)
Third		48	23 (48%)
Stokes-Adams attacks in 11 cases.			
Mortality—40 deaths (16 autopsies)			42%

The differences between this group of cases of recent infarction and the average of all cases of cardiac infarction in hospital are discussed in the text.

are small. Recent infarction was the cause of the heart block in almost half of these, suggesting that if ECG records were taken as frequently in other forms of heart disease the numbers in this group would increase accordingly.

An attempt was made to segregate the cases of recent cardiac infarction showing heart block. These were reasonably certain clinically proved cases (Table X). It can be seen at once that the 96 patients in this group were older than the average of those with recent infarction and that the proportion of females and of those receiving digitalis was also greater. These factors, along with the heart block, are largely responsible for the higher than average mortality in this "poor risk" group.

TABLE XI.—DIGITALIS CAUSING HEART BLOCK

	Cases	*Total*	*%*
First-degree block	157	255	62
Second-degree block	35	73	47
Third-degree block	29	95	30
Whole series	190	349	55

Digitalis causes a greater proportion of the lesser degrees of block.

An attempt was made to ascertain the cause of the heart block in each case of the series (Tables XI to XVIII). It is seen that digitalis was considered the likely cause of the heart block in 55% of the 349 patients. In all probability this is the result of the predominance of the older age groups and the frequency of congestive heart failure. Digitalis is more likely to cause the lesser degrees of heart block. Recent cardiac infarction was considered the

TABLE XII.—RECENT CARDIAC INFARCTION CAUSING HEART BLOCK

	Cases	*Total*	*%*
First-degree block	51	255	20
Second-degree block	28	73	38
Third-degree block	48	95	50
Whole series	96	349	27.5

Recent infarction causes a greater proportion of the higher degrees of block.

TABLE XIII.—ARTERIOSCLEROTIC HEART DISEASE CAUSING:

	Cases	*Total*	*%*
First-degree block	5	255	2
Second-degree block	8	73	11
Third-degree block	19	95	20
Whole series	29	349	8

Arteriosclerotic heart disease causes a greater proportion of the more severe grades of block.

cause of heart block in 27.5% of the 349 patients. It was responsible for a higher proportion of the more severe degrees of block, amounting to fully half of those showing complete heart block.

Arteriosclerotic heart disease (which likely includes several cases of old cardiac infarction) was the apparent cause of the heart block in 8% of the 349 patients. Its influence was greater in those with the more severe degrees of block.

TABLE XIV.—ACTIVE RHEUMATIC FEVER CAUSING:

	Cases	*Total*	*%*
First-degree block	14	255	5.5
Second-degree block	2	73	2
Third-degree block	0	95	0
Whole series	15	349	4

When children are excluded, the higher grades of block are seldom encountered in acute rheumatic fever.

Active rheumatic fever (Table XIV) does not play a large role in causing heart block when children are excluded from the study. Prolongation of the PR interval is the chief form of block found in acute rheumatic fever in the adult.

TABLE XV.—AORTIC STENOSIS CAUSING:

	Cases	*Total*	*%*
First-degree block	13	255	5
Second-degree block	1	73	1
Third-degree block	8	95	8
Whole series	19	349	5.5

Aortic stenosis is an important cause of complete heart block.

Aortic valve disease is an important cause of heart block, probably because of the proximity of the bundle of His. Aortic stenosis and/or insufficiency (Tables XV and XVI) were responsible for all grades of block with approximately equal frequency, except that aortic stenosis was the cause of a higher proportion of complete heart block than of lesser degrees of block.

TABLE XVI.—AORTIC INSUFFICIENCY CAUSING:

	Cases	*Total*	*%*
First-degree block	4	255	2
Second-degree block	2	73	2
Third-degree block	3	95	3
Whole series	7	349	2

Aortic insufficiency was not an important cause of heart block.

TABLE XVII.—MYOTONIA ATROPHICA CAUSING:

	Cases	*Total*	%
First-degree block	3	255	1
Second-degree block	1	73	1
Third-degree block	0	95	0
Whole series	4	349	1

The lesser degrees of heart block seem to be affected here.

Lastly, among the uncommon causes of heart block were myotonia atrophica in four cases (Table XVII), toxic myocarditis, myocardial fibrosis, and Marie-Strümpell spondylitis in one instance each (Table XVIII). Myotonia atrophica is apparently more apt to cause the lesser degrees of block, while all grades of block may be encountered in diffuse myocardial processes.

TABLE XVIII.

Toxic myocarditis	1
Diffuse fibrosis of myocardium (autopsy) (all 3 degrees of block)	1
Marie-Strümpell spondylitis	1

The upper septum and region of the aortic valve are particularly apt to be affected in diffuse processes involving the myocardium.

DISCUSSION

In the search for the probable cause of prolonged AV conduction, in some cases of this series, one was impressed by the prominence in the clinical picture of such symptoms as nausea, vomiting and/or diarrhea. A strong vagal effect and loss of potassium may possibly be contributing factors here, either alone or potentiating the action of digitalis.

Certainly there were many examples in this series of unusual sensitivity to digitalis or one of its purified glycosides. It seems apparent that in many older patients with congestive failure, digitalis leaf in doses of three grains three times daily for three days, as recommended in standard teaching for many years, is grossly excessive. There were instances in which such large doses of digitalis were ordered when the patient had already been receiving the drug either prior to admission to hospital or as emergency treatment on admission.

A further impression gained from study of these cases was that the initial ECG record, although ordered and taken promptly enough, was at times not viewed or heeded until initial large doses of digitalis had produced block or had accentuated a pre-existing conduction defect. Particularly did this seem important in older patients with congestive heart failure, some of whom were quite sensitive to the drug.

An attempt to denote physical signs of some importance in diagnosis of heart block in these cases proved a failure. Triple or gallop rhythm was frequently recorded but was likely due to the atonic ventricles of congestive failure rather than to prolonged conduction. Similarly, the "bruit-de-canon" in complete heart block, when recorded, did not seem to be relied upon by the historian in differential diagnosis.

Variation in AV conduction has importance in relation to prognosis and to the dramatic clinical episodes called Stokes-Adams attacks. There is general agreement that the prognosis of heart block depends upon the etiology of the underlying heart disease. When acute infection, fresh infarction, or intoxication such as that due to digitalis excess is the cause of the block, the latter usually clears if the patient survives the acute episode.

SUMMARY AND CONCLUSIONS

The clinical records of 349 cases of prolonged AV conduction observed between 1949 and 1956 on the public wards of the Toronto General Hospital have been studied.

Summaries have been given of the incidence of the three degrees of block along with the details of the electrocardiographic (ECG) findings, the age distribution, the various forms of heart disease present, the probable cause of the heart block, the frequency of congestive heart failure and of Stokes-Adams attacks, and mortality figures.

Comment has been made on the prominence of nausea and vomiting and/or diarrhea in some cases and their possible contribution to increased digitalis sensitivity.

Suggestions resulting from this study include: (a) due caution should be observed in digitalization of older patients with congestive failure; (b) more frequent ECG records should be made in the initial phases of digitalization to detect undue sensitivity to the drug.

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THE RESPIRATORY UNIT AT THE TORONTO GENERAL HOSPITAL*

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IN THE Toronto General Hospital, patients with severe respiratory insufficiency were treated, until 1958, without any special facilities on the ward to which they had been admitted. Tank respirators and cuirass respirators were used, and the results were often unsatisfactory. A group of staff physicians was appointed to make recommendations to improve this situation. As a result of these recommendations a special respiratory unit was established to which patients with severe respiratory insufficiency might be referred.[1] The patients admitted to the unit are all very seriously ill and are in respiratory failure. Most would die if not treated with assisted ventilation. The types of patients admitted are those with crushed chest with paradoxical respiration, those with neurological disorders causing paralysis of the respiratory muscles, patients in deep coma due to barbiturate poisoning with respiratory failure, patients whose respiration has failed after an operation, and patients suffering from chronic pulmonary disease with carbon dioxide narcosis.

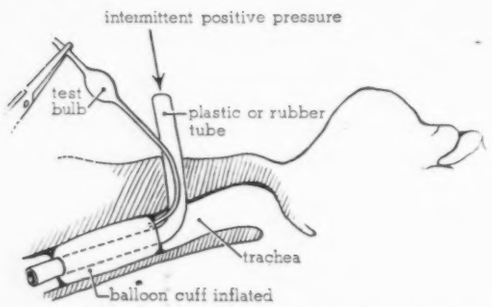

Fig. 1.—Diagram of trachea with tracheotomy tube and inflated cuff.

There are four specialist physicians in clinical charge of the unit: an anesthetist whose main interest is in ventilation; an otolaryngologist whose concern is tracheotomy and its care; a neurologist, because many of the patients have respiratory insufficiency due to neurological causes; and an internist whose particular interest is in chest disease and respiratory function. All four contribute to the management of every patient. A year ago a full-time research fellow was appointed to the unit, and he acts also as a resident. Patients may be admitted to the unit by one of the four staff physicians.

The unit is permanently staffed by a specially trained group of graduate nurses. There is one nurse for each patient and a head nurse in charge who does not look after any individual patient. These nurses have considerable responsibility, as they must recognize trouble early, know what to do about it and do it quickly.

*This paper was presented at the Annual Meeting of the Canadian Thoracic Society, Ottawa, June 29, 1960.

The original unit consisted of four beds in a room with a central partition. Recently this has been increased to six beds in two rooms. Eleven beds are planned for the future in an especially designed area.

Intermittent positive pressure machines are used to ventilate the patients. For short-term treatment (less than 24 hours) the machine is connected to a cuffed orotracheal tube; for long-term treatment, to a cuffed tracheostomy tube (Fig. 1). The lungs

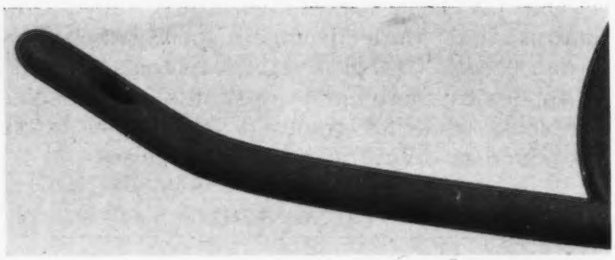

Fig. 2.—Curved-tip catheter for bronchial suction.

are inflated by air or an oxygen mixture from the machine under pressure; the machine then shuts itself off and expiration is passive. Many different machines are available. It is possible to set the volume of gas for each breath, the rate of respiration and the rate of flow of gases into the lung. In patients who have some spontaneous but inadequate respiration, one may use machines which the patient triggers with his own inspiration, thus eliminating the difficulty of the patient breathing against the machine. Machines vary in versatility and reliability, and the most suitable type of machine is selected for the individual problem.

The bronchial tree must be kept free of secretions. The nurses are trained to use special curved-tip catheters (Fig. 2). These are necessary for suction of the left lung, as straight catheters almost invariably will enter the right lung only.[2] Clearing the secretions is aided by enthusiastic and regular physiotherapy.

The advantages of intermittent positive pressure respiration are that it is applicable to any type of respiratory insufficiency and it permits easy and thorough clinical examination, physiotherapy and satisfactory nursing (Fig. 3). The disadvantages are

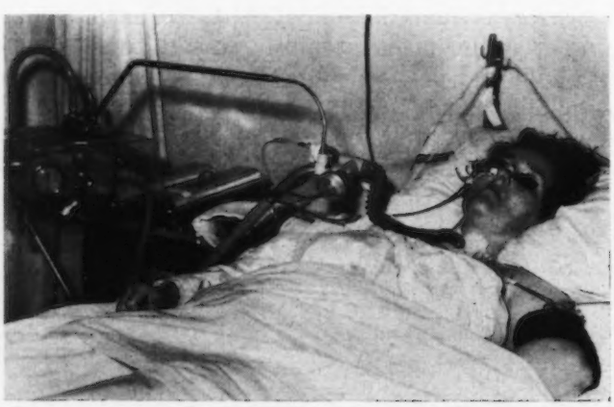

Fig. 3.—Patient being ventilated by an intermittent positive pressure machine. There is easy access for clinical examination and nursing procedures.

that experience is necessary for running the machines; the tracheostomy and the cuffed tube require care, especially in the prevention of tracheal ulceration; and adequate humidification of the inspired gases is necessary. The successful use of intermittent positive pressure respiration depends on constant attention to details and upon the prompt recognition and correction of any deviation from the usual.

In following the progress of these very ill patients, one depends on the general appearance, half-hourly pulse and blood pressure readings and physical examination of the chest. Attention is paid to the appearance of the bronchial aspirate.

Measurements of respiratory rate, minute volume and tidal volume are made by introducing a small gas meter into the circuit (Fig. 4). Measurements are made every 15 minutes or even more frequently when the patient is first admitted. The best check for the adequacy of ventilation is estimation of arterial blood carbon dioxide tension, and this is done at least once a day in the more difficult cases.

As the patient improves, his ability to do without the machine is assessed by ventilation measurements and he is gradually weaned off assisted respiration.

Throughout the patient's course one must know what is happening. One must measure ventilation and be sure that this ventilation is producing adequate elimination of carbon dioxide.

In October 1958, the first patient was admitted to the unit, and by March 1960 (that is, 18 months later) there had been 100 admissions (Table I). Of this total of 100 admissions, 76 patients have recovered.

TABLE I.—DIAGNOSIS AND SURVIVAL OF 100 ADMISSIONS

Diagnosis	*Total*	*Survived*
Crushed chest	10	8
Neurological disorders	28	23
Barbiturate overdosage	16	15
Postoperative respiratory failure	18	12
Chronic pulmonary disease	25	17
Miscellaneous	3	1
Total	100	76

There have been 10 patients with crushed chests and gross paradoxical respiration of whom eight recovered. Intermittent positive pressure is used to ventilate the patients until the rib fractures heal. It is no longer necessary to use hooks through the chest with weights to stabilize the chest wall. This is now stabilized by means of intrathoracic positive pressure. One of these patients was a 54-year-old man who was thrown from his horse. He sustained multiple injuries with flail chest and bilateral pneumothoraces. He was treated by bilateral closed intercostal catheter drainage, tracheotomy and intermittent positive pressure, and was discharged from the unit after 15 days.

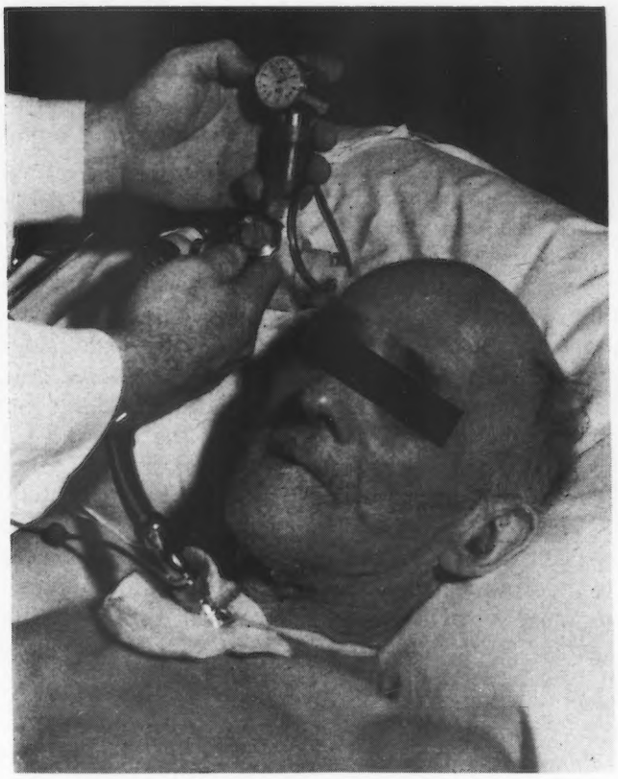

Fig. 4.—Wright respirometer being used to measure ventilation. It is only slightly larger than an ordinary watch.

Twenty-eight patients had primarily neurological disorders and 23 survived (Table II). An example was a 54-year-old man living in northern Ontario, who developed polyneuritis which over a month progressed to complete paralysis including even his facial muscles. When he developed trouble breathing and swallowing, he was transferred 450 miles to the unit in Toronto. He had pneumonia and was very emaciated and moribund. Tracheotomy was carried out, he was ventilated using intermittent positive pressure, and the bronchi were cleared of secretions by adequate catheter suction. He was sent home after four weeks much improved, and when seen recently had completely recovered.

TABLE II.—TYPE OF NEUROLOGICAL DISORDER AND SURVIVAL OF 28 PATIENTS

Neurological disorders	*Total*	*Survived*
Tetanus	1	0
Poliomyelitis	1	1
Polyneuritis	4	4
Myasthenia gravis	7	6
Cord injury	7	6
Status epilepticus	3	2
C.N.S. lesions	5	4

Barbiturate overdosage is the easiest of these problems to manage, as the patients usually have normal lungs and require ventilation for comparatively short periods. Those who have taken a short-acting barbiturate can be treated by an orotracheal tube, and tracheotomy is not necessary. Of the 16 patients treated only one died, and this patient had severe hypoxia and hypotension before admission.

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There were 18 cases of postoperative respiratory failure. Some had had previous lung disease. Others developed pulmonary trouble after operation. Twelve recovered. One of these was a 19-year-old boy operated upon for a large atrial septal defect of the primum type, using the heart-lung pump. Postoperatively he developed an extensive staphylococcal pneumonia and severe respiratory insufficiency. Tracheotomy and intermittent positive pressure breathing were performed, and he improved during that day. That evening he developed a tension pneumothorax on the right side. This was treated by an intercostal catheter and Emerson pump suction. Ventilation had to be greatly increased because much of the inspired air bubbled out of the bronchopleural fistula. After seven days, during which time he was desperately ill, he began to improve, and then developed a tension pneumothorax on the left side. This was treated in the same way. He now had two pneumothoraces with two bronchopleural fistulae with suction pumps. By using a high volume machine it was possible to maintain ventilation. He recovered and was sent home after six weeks. He was seen some months later, and had remained well.

TABLE III.—TYPE OF CHRONIC CHEST DISEASE AND SURVIVAL OF 19 PATIENTS

Chronic pulmonary disease	*Total*	*Survived*
Emphysema	*17 (23)	9 (15)
Bronchiectasis	1	1
Status asthmaticus	1	1

*Figures in parentheses indicate number of admissions.

Patients with chronic pulmonary disease made up about a quarter of the cases, some being admitted several times (Table III). Those with emphysema presented the greatest difficulties. Nine of 17 with this disorder survived. Such patients are usually unconscious and often elderly and debilitated. They are difficult to ventilate, as it often requires great pressure to distend the lungs. If one uses sufficient pressure to obtain adequate ventilation, this may impede venous return, causing right heart failure, followed by a fall in blood pressure and death. One often must adopt a middle course, using ventilation sufficient to keep the patients alive but insufficient to upset the delicate cardiac status. In addition these patients develop many complications such as bleeding peptic ulcer, paralytic ileus and spontaneous pneumothorax. Nearly all the patients who survive return to worthwhile although limited lives. One cannot predict on admission which patients will do well and which will die. For example, a 53-year-old man with advanced emphysema was admitted with pulmonary infection, right heart failure causing edema up to the axillae and a very large liver. In spite of antibiotics, diuretics, digitalis and intermittent oxygen, he deteriorated and became semiconscious. Tracheotomy was performed and adequate ventilation instituted. He made a gradual recovery, losing 40 lb. of edema fluid. Intermittent positive pressure ventilation was stopped after about two weeks, and he did very well thereafter.

In a miscellaneous group of three patients, there was an 81-year-old man who took carbolic acid and then attempted to drown himself. He did not survive. There was a patient with acute nephritis and hyperkalemia who died 17 hours after admission. The third patient was a 16-year-old boy who developed an influenza-like illness followed by bilateral extensive staphylococcal pneumonia. Tracheotomy was performed because of episodes of subacute respiratory obstruction due to thick secretions and clots. One morning in the unit he suddenly manifested obvious air hunger and became unconscious. One member of the clinical team was present and bronchoscoped him through the tracheotomy, and using forceps removed a large blood clot obstructing the carina. He required some respiratory assistance, but did well and was sent home after three weeks. This case emphasizes the importance of rapid recognition of respiratory failure, and of the availability of instruments and personnel for immediate treatment which may be life-saving.

The admission rate in the unit has been gradually increasing. At first there was a new patient approximately every 10 days, and now on the average there is one every three days. About 20% of patients come from other hospitals or other towns. On one occasion a member of the team went as far as Mattawa (250 miles from Toronto) to transport a young man with a crushed chest. He was brought by ambulance, and was ventilated by a portable intermittent positive pressure machine connected to an orotracheal tube. Patients may be safely transported any distance provided an airway is maintained, provided suction can be performed and provided there is some means of ventilating the patient.

In many conditions such as those already mentioned, inadequate ventilation which cannot be relieved by the administration of oxygen is the immediate cause of death. In many, the primary condition is potentially reversible provided one can keep the patient ventilated. Even in patients who are moribund, the institution of adequate ventilation may cause striking improvement and eventual return to normal life.

SUMMARY

A unit for the treatment of severe respiratory insufficiency was created at the Toronto General Hospital in October 1958. In clinical charge of the unit is a team of four specialist physicians: an anesthetist, an otolaryngologist, a neurologist and an internist. Specially trained nurses are essential. Respiration is maintained by intermittent positive pressure machines connected to cuffed orotracheal or cuffed tracheotomy tubes. The advantages of intermittent positive pressure respiration are that it is applicable to any type of respiratory insufficiency and it permits easy and thorough clinical examination, physiotherapy and satisfactory nursing.

The types of cases admitted were crushed chest, neurological disorders, barbiturate poisoning, post-operative respiratory failure, and chronic pulmonary disease with carbon dioxide narcosis.

Of the first 100 admissions, 76 patients recovered. The patients were all seriously ill, and most would have died if not treated by assisted ventilation. In many patients the primary condition was reversible, and the institution of adequate ventilation caused striking improvement and eventually a return to normal life.

Since the presentation of this paper, the management of the patient with respiratory insufficiency has been extensively described by H. B. Fairley and R. A. Chambers in the *Canadian Anaesthetists' Society Journal*, 7: 447, 1960.

The author wishes to acknowledge the contribution of his colleagues on the attending staff of the Respiratory Unit: Drs. H. O. Barber, R. A. Chambers and H. B. Fairley; and of the Research Fellow to the Unit, Dr. M. Mendelson.

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ALLERGY TO RAW COFFEE – AN OCCUPATIONAL DISEASE*

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ONE OF US (M.K.), on becoming associated with a coffee manufacturing plant on a part-time consulting basis, was surprised to learn that reactions, probably allergic in type, were occurring in a proportion of the workers.

The plant nursing personnel were aware that the symptoms complained of by affected workers were predominantly those due to air-borne material and involved the eyes, nose and lungs. The sole source of such material was the coffee which is brought into the plant as raw green beans. Bags containing the beans are emptied manually and the chaff is separated from the bean mechanically. Considerable very fine, dusty powder is released into the air during this process, and many of the workers had noted appearance or aggravation of their symptoms when working in this area. The green beans are conveyed to the roasting pans, roasted, packed and sealed. Little or no discomfort had been noted in the packing or dispatching areas. With this preliminary knowledge, the raw coffee was considered to be the likely allergen.

A few case reports of occupational coffee bean allergy have appeared in the literature, but no large series of cases has previously been reported.[1-3] Figley and Rawling[1] in their report of seven cases found that the burlap bags used to transport the coffee beans were contaminated with castor bean. On the basis of positive skin tests to castor bean and of Schultz-Dale studies, they came to the conclusion that the castor bean allergen was responsible for the symptoms in their patients. This possibility has been excluded in our study by careful inquiry into the methods of shipping the beans from South America. New bags are used, and at no time during transportation do the coffee beans or the bags come in contact with castor beans or fertilizer made from castor beans.

METHOD OF STUDY

Aqueous extracts of raw chaff, raw beans, roasted chaff and roasted beans were prepared in the Allergy Laboratory of the Montreal General Hospital and standardized by the method of Cooke and Stull[4] to contain 1, 10, 100 and 1000 protein nitrogen units (P.N.U.) per millilitre. Phenol 0.4% was included as a preservative. Intradermal testing on the arm, using 0.025 ml. of each extract, was carried out. All testing was carried out by the nurses, and after 15 minutes the size of any wheal was read by the physician, using a plastic rule with graduated circles of 4, 8, 10, 12 and 20 mm. diameter. If wheals with pseudopods occurred, no further testing was carried out with that particular extract. In the absence of pseudopods all subjects were tested with the four extracts at the four different strengths.

The personnel to be tested were subsequently divided into three groups but were selected initially as a whole by the nurses from the general worker population. These groups were: (1) 17 subjects who had had absolutely no contact with coffee manufacturing in the plant—these were usually new employees or office personnel; (2) 39 subjects suspected by the nurses to have allergic symptoms; (3) 56 subjects working in the plant and usually, but not always, having had contact with the raw and prepared coffee but who had no symptoms. This latter group included 17 subjects whose contact with the coffee processing had been extremely brief.

Immediately before skin testing, the plant physician, who until that time had not met any of the workers and was unaware of their individual complaints, took a brief history directed at eliciting allergic symptoms to coffee and including a previous history of asthma, hay fever, hives, bronchitis, sinusitis and eczema in the subject or his immediate family. Each person was then arbitrarily classified as allergic to coffee, not allergic, or not allergic and with no contact with coffee. This initial, entirely

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†With the assistance of Mrs. C. Thompson, R.N., and Mrs. C. Steele, R.N.

TABLE I.—SYMPTOMS OF COFFEE ALLERGY IN ORDER OF FREQUENCY

Symptom	Number of Subjects Showing Each Symptom: Group 2 — 39 subjects allergic by history	Group 3 — 56 subjects not allergic by history
Nasal congestion and discharge	29	—
Dermatitis	19	2
Dyspnea	18	—
Asthma	16	—
Sore eyes with lacrimation	14	—

clinical grouping led to the subdivision of the personnel as described above. Immediately after such categorization, the skin testing was performed. Both males and females were studied. All were adults of various ages and none were taking any medication at the time of testing.

Results

The symptoms in Groups 2 and 3 are shown in Table I. Subjects in Group 1 who had never been in contact with raw or roasted coffee had no symptoms.

TABLE II.—FREQUENCY OF WHEALS WITH PSEUDOPODS IN EACH OF THE THREE GROUPS TESTED

Group	No. in group	No. with pseudopods	%
I. No contact	17	0	0
II. Allergic by history	39	27	69
III. Not allergic by history	56	8	14

The presence of a wheal with pseudopods was considered a significantly positive reaction at any testing strength employed. Some individuals gave such reactions with the 1 P.N.U. extracts, though most in whom they appeared required the 10 P.N.U. or more to elicit pseudopods. Their frequency is shown in Table II.

TABLE III.—NUMBER OF SUBJECTS SHOWING WHEALS WITH PSEUDOPODS

Extract tested	Group 2 — 39 subjects allergic by history		Group 3 — 56 subjects not allergic by history	
Raw chaff	26	69%	7	12%
Raw bean	18	46%	1	2%
Roasted chaff	3	8%	0	—
Roasted bean	1	2%	0	—

Table III shows that the positive reactions were almost limited to the raw chaff and raw bean extracts and were predominantly found in the allergic group. Almost all pseudopods from the raw bean, roasted bean and roasted chaff were in subjects having positive reactions to raw chaff. To confirm that the reaction to raw bean was not due to contaminating raw chaff, several beans were carefully separated by dissection from their outer coverings and an aqueous extract was prepared. This extract, when tested by passive transfer against the serum of an individual who was known to react on direct skin test to the regular raw bean extract, again gave a positive reaction.

The significance of the fact that a worker or any close member of his family suffered from asthma, hay fever, sinusitis, eczema, hives or bronchitis unrelated to contact with coffee was studied. Of subjects who were allergic to coffee by history, and who also had wheals with pseudopods on skin testing, 20 out of 27, or 74%, had a positive personal or family history. In contrast, of 65 subjects who neither had an allergic history to coffee nor pseudopods on testing, the personal or family history for the above conditions was positive in only 31, or 48%. The importance of the previous personal or family history was brought out further by analysis of the reactions in individual cases as shown in Table IV. Although the groups are small, they do suggest that an individual who has suffered from asthma, bronchitis or, to a lesser extent hay fever, is very likely to develop allergic symptoms to coffee. This is less likely if only the family history is positive. The presence of two of these three factors in his personal history, or one in his personal and one in his family history, results in an almost 100% incidence of coffee allergy.

DISCUSSION

The results of this investigation have confirmed the presence of allergy to raw coffee in a selected group of workers. As the total worker personnel approximates 400, at least 10% have developed allergic symptoms. This is a minimum, as not all the workers were questioned or skin-tested, and in addition, some have had negligible contact with the raw coffee area. Although sensitization to both raw chaff and green bean has been demonstrated, there is little likelihood of dust being produced from the bean itself. It is probable that one or more common antigens are shared by both the raw chaff and raw bean, thus giving positive skin tests to both, although only the chaff dust was responsible for the sensitization. In view of the incidence of symptoms, the chaff is clearly a potent allergen. It is of interest that none of the allergic personnel,

TABLE IV.

	Asthma		*Bronchitis*		*Hay fever*		*Sinusitis*		*Hives*		*Eczema*	
Number of subjects in all groups with a personal history of	7		10		7		14		5		6	
Number of above who are allergic to coffee by history	6	85%	9	90%	5	71%	7	50%	2	40%	1	17%
Number of subjects in all groups with a family history of	13		13		9		3		4		5	
Number of above who are allergic to coffee by history	7	54%	9	69%	1	11%	1	33%	3	75%	2	40%

with one possible exception, had any symptoms associated with taking coffee as a beverage. The negative skin tests to the roasted bean indicates that the antigenic structure was changed during the roasting and the finished product would be similarly altered and rendered non-allergenic.

Methods of reducing the content of chaff dust in the air are at present under study, as is the possibility of desensitizing those personnel with the more severe symptoms. Employment in the future of workers who do not have any previous history of asthma, hay fever or bronchitis will also reduce the incidence of clinical allergy. Further work is at present in progress to define the chemical moieties in the chaff responsible for its antigenicity.

SUMMARY

Allergic reactions to the chaff of the raw coffee bean have been demonstrated. These mainly take the form of coryza, dermatitis, lacrimation and bronchial obstruction, and are due to contact with chaff dust in the air and respiratory passages. Methods of control are under study.

We wish to thank Mrs. Judith H. Rollins, who prepared the extracts used for skin testing.

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THE CONTROL OF PULMONARY VENTILATION IN PHYSIOLOGICAL HYPERPNEA*

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THE IDENTIFICATION of the factors responsible for the control of pulmonary ventilation has been a subject of interest to physiologists for at least one hundred years. Research in this field has contributed a great deal to our knowledge of respiratory physiology. Most of the evidence upon which this knowledge is based is concrete and indisputable, although some of it is circumstantial and indirect. However, a great deal of speculation has been, and is, accepted as fact; and some illogical conclusions have been deduced from experimental data. Much of the literature on the subject is contradictory;[41] and it is unfortunate that after 50 years of intensive investigation, our knowledge of this important subject is still far from complete.

THE CLASSICAL THEORY AND ITS DISCREPANCIES

It is generally stated that the control of pulmonary ventilation under normal physiological conditions is carried out through the action of carbon dioxide on the respiratory centre. This theory, although still unproved, was firmly established by Haldane,[100–104] who demonstrated beyond doubt that carbon dioxide (CO_2) is a powerful respiratory stimulant. Since the time of Haldane's classical work, the evaluation of experimental data and the evolution of thought have tended to support the hypothesis that the tension of carbon dioxide in the arterial blood ($paCO_2$) is the major factor controlling the volume of pulmonary ventilation.[12, 46, 56, 57, 95, 101, 189] It has been shown that the arterial tension of oxygen (paO_2) and the pH of the arterial blood may play a role in the increase in volume of pulmonary ventilation under certain abnormal conditions;[102, 142, 150] and it has been suggested that they play a significant role in the normal physiological state.[13, 83, 84, 95, 120, 189] For the past 30 years assessment of the role of the classical stimuli, pCO_2, pO_2 and pH, has dominated the thinking of the majority of physiologists; and there has been considerable controversy concerning the importance of each.[6, 12, 32, 45, 46, 83, 84] It has been recognized by a few that the theory is deficient in many respects,[41] but much of the literature tends to emphasize the desirability of integrating experimental data with the classical hypothesis. Although minor modifications have been proposed, the basic tenets of the classical theory are still generally accepted despite many observations which tend to discredit it. The evidence in favour of this theory has been reviewed recently by Gray,[95] who has quantitated the ventilatory response to artificially induced changes in these three stimuli. His thesis is that the normal physiological stimulus of the respiratory centre is the arterial tension of carbon dioxide, aided by changes in pH when these occur, and by hypoxia on occasion. He has derived an equation which quantitates and predicts the respiratory response to these stimuli when changes are induced in them either singly or in combination. Minor modifications of Gray's equations have been proposed,[45, 47, 135] but little attention has been directed to an assessment of the adequacy of the theory as a whole.

Most of the investigative work on the problem of identifying the factors which control pulmonary ventilation has been concerned with the respiratory response to artificially induced changes in $paCO_2$, paO_2 and arterial pH in resting subjects. An induced change in one of these stimuli certainly evokes a respiratory response, but the assumption that these

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stimuli also regulate the activity of the respiratory centre under physiological conditions may not be valid. Tacit insistence upon the necessity of this assumption tends to encourage acceptance of the theory. Although this approach to the study of respiration is useful and productive, it must be recognized that artificial change in these stimuli is unphysiological; and the application of data obtained in this manner to physiological states implies that these same mechanisms are operative. If this implication is true, it should be possible to demonstrate similar changes in these stimuli when a physiological increase in pulmonary ventilation occurs during muscular exercise. Such changes have not been clearly demonstrated.

Unfortunately, neither the present theory, nor any yet offered, can provide an explanation for all, or even a large part, of the hyperpnea of muscular exercise. Inspired carbon dioxide in air can produce a maximum ventilatory response of approximately 70 litres per minute with a concomitant increase in $paCO_2$ of 20 mm. Hg in the normal subject at rest.[14, 91, 95] However, the ventilatory response to the stimulus of muscular exercise may exceed 100 litres per minute with a very small, if any, change in $paCO_2$,[12, 14, 41, 104, 126, 133, 146] and there is general agreement that there is little or no change in arterial pCO_2 during exercise in normal subjects under normal conditions.[3, 4, 12, 17, 23, 36, 44, 61, 82, 97, 126, 137, 146, 179, 189] It has been demonstrated that either a low arterial pO_2 or a decrease in pH of the arterial blood will produce an increase in pulmonary ventilation, but the magnitude of these responses is small.[27, 29, 43, 60, 95, 102, 105, 117, 121, 139, 140, 150, 155, 164, 189] There is no evidence that there is either a decrease in paO_2 or a significant change in the pH of the arterial blood in normal subjects during muscular exercise under normal conditions.[4, 6, 27, 41, 104, 111, 124, 146]

The theory is even less satisfactory when one considers it in relation to pathological conditions in which hyperventilation occurs. There is no general agreement on what factors are responsible for the hyperventilation observed both at rest and during exercise in patients suffering from cardiac and pulmonary diseases.[37, 38] Changes in arterial pCO_2, pO_2 and pH, sufficient to cause the degree of hyperventilation observed in these patients have not been demonstrated. The $paCO_2$ is actually below normal in subjects who hyperventilate,[48] the change in pH is small and inconstant, and a significant consistent decrease in arterial pO_2 has not been shown.[25, 119] Nevertheless, a hypothetical change in one or more of the classical stimuli, or in the sensitivity of the respiratory centre to these stimuli, is usually invoked to explain it.

Despite these discrepancies, the classical theory is still generally accepted, and some particular aspect of it is usually invoked to explain hyperpnea and hyperventilation.

Since muscular exercise can increase pulmonary ventilation to a greater degree than is possible by means of artificial changes in the classical stimuli without an appreciable change in any of them, and since hyperventilation is observed in pathological states with a low arterial pCO_2, a normal or even high pH, and a variable paO_2, it is necessary to postulate one of two possibilities:

1. There is some mechanism "sensitizing" the respiratory centre to these three; or
2. PCO_2, pO_2 and pH are not the only effective stimuli of the respiratory centre under physiological conditions; and there is some other factor or factors, at present unknown, which are active in the control of pulmonary ventilation.

OTHER FACTORS WHICH INFLUENCE RESPIRATION

Peripheral stimuli, including stretch and possibly metabolic receptors in the limbs and muscles, have been shown to cause a small but inconsistent increase in pulmonary ventilation.[3, 16, 17, 21, 40, 41, 56, 57, 107–109] However, there is general agreement that the contribution of these stimuli to the hyperpnea of muscular exercise is negligible.[8, 40, 41, 153] Krogh and Lindhard postulated cortical irradiation of impulses from the motor cortex to the respiratory centre as an important factor, but this suggestion has been disproven recently by Kao *et al.*[127] The pressoreceptors of the carotid sinus and aortic arch are known to influence respiration, but the effect of these is thought to be small.[189] There is evidence that pressoreceptors located in the great veins, in the right side of the heart, and in the pulmonary artery have an effect on respiration,[41, 109, 143, 145, 188] but the magnitude of their response to stimulation is uncertain. In addition, several other types of receptors have been described in the pulmonary vasculature and in the right side of the heart.[55] None of these have been shown to stimulate respiration, but all of them seem to cause apnea when under the influence of certain drugs. Whether this is a paralytic effect is unknown. It is a common observation that pulmonary vascular congestion causes hyperventilation; this phenomenon has been ascribed to reflexes arising from somewhere in the lung,[37, 53, 67] but the existence and possible location of these receptors is uncertain.[38, 112, 162, 172] Finally, a rise in body temperature increases respiration to some extent, but the change in temperature during muscular exercise is too small, too slow and too inconstant to be a major factor in the control of pulmonary ventilation.[41]

In addition to the classical stimuli, there are, therefore, many proven and several hypothetical factors which influence respiration. The ventilatory responses produced by most of them are thought to be small, and their role in the control of pulmonary ventilation during muscular exercise is considered to be a minor one.

PLAN OF THIS INVESTIGATION

Any acceptable theory of control of pulmonary ventilation must be capable of explaining hyperpnea under all physiological conditions in both normal and abnormal subjects. Since muscular exercise is the most physiological respiratory stimulus, it seems that one of the best methods of studying the

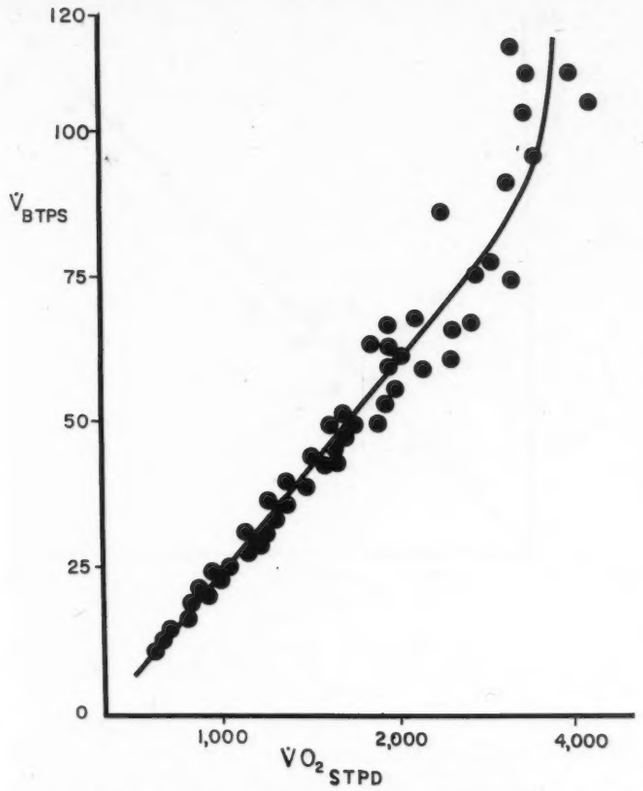

Fig. 1.—The relationship between oxygen consumption in ml. per minute ($\dot{V}O_{2STPD}$) and minute ventilation in litres per minute ($\dot{V}_{BTPS}$) at different levels of exercise. The graph represents a collection of 600 determinations in 85 subjects as reported in the literature.

physiology of respiration is through an investigation of the effect of exercise upon pulmonary ventilation. It seems advisable, therefore, to attempt to determine the adequacy of the classical theory in the control of the hyperpnea of exercise in both normal and abnormal subjects.

There are many difficulties both theoretical and practical in this approach to the study of the physiology of respiration. Not the least of these difficulties is the problem of relating the exercise stimulus to the respiratory response in different individuals under varying conditions. Since the effect of muscular exercise on pulmonary ventilation depends upon the degree of muscular activity, some parameter which relates the respiratory response to the exercise stimulus is desirable, and perhaps necessary, in the investigation of respiratory physiology. It has been shown that the oxygen consumption per minute ($\dot{V}O_2$) is proportional to the physical work performed by an individual for a specific type of muscular activity.[106] One may therefore quantitate the work performed by measuring the $\dot{V}O_2$; the ventilatory response to the work stimulus may be obtained by measuring the minute ventilation ($\dot{V}_{BTPS}$). The accompanying figure (Fig. 1) is a composite graph of 600 determinations of $\dot{V}O_2$ and $\dot{V}_{BTPS}$ reported in the literature. This graph suggests that the minute ventilation is proportional to the oxygen consumption per minute. The calculated line is straight except in the higher range of exercise, and if projected it will pass through the origin of the graph. The slope of this line (i.e. $\dot{V}_{BTPS}$ divided by $\dot{V}O_2$) is a mathematical description of the position of the curve and an expression of the rate of change of the respiratory response to the exercise stimulus. The calculation which expresses the slope of this line is the oxygen ventilation equivalent (O_2V). If this proportionality between minute ventilation and oxygen consumption per minute can be shown to exist in single subjects at various levels of exercise, then the problem of relating the respiratory response to the exercise stimulus may be simplified. If this can be established, then the oxygen ventilation equivalent may be useful in the investigation of respiratory physiology. This parameter may be a means of comparing respiratory activity with changes in the classical stimuli, and with any other factors which might be considered to influence the ventilatory response during exercise. The purpose of this investigation is to study the exercise stimulus-response curves of normal and abnormal subjects, to test the validity of O_2V as a quantitative expression of respiratory activity, and if possible to use this parameter to assess the adequacy of the classical theory.

MATERIAL AND METHODS

In this investigation 715 experiments were carried out on 151 persons. Of these, 17 were normal subjects and 134 had either cardiac or pulmonary disease. The range of clinical material is large and representative of a wide variation in cardio-pulmonary status.

All observations were carried out during exercise on a motor-driven treadmill. The subject walked for six minutes breathing either room air, or approximately 0.05% carbon monoxide in air, or approximately 2% carbon dioxide in air. The dead-space of the high velocity Robinson valve, which was used in all of these experiments, was 85 c.c. The speed was kept constant at a comfortable pace for each individual, and the work was increased by altering the slope of the treadmill. During the sixth minute of exercise, the expired air was collected in a Douglas bag, and its concentration of oxygen and carbon dioxide was determined in the Haldane apparatus. Duplicate Haldane analyses were required to check within 0.04 vol. %. The volume of expired air was measured by displacement into a Tissot spirometer. The $\dot{V}O_2$ was calculated at standard temperature and pressure, dry; and the minute ventilation is expressed at bo temperature, ambient pressure, saturated. Exactly similar determinations were carried out during the fifth minute of exercise as a check upon the attainment of a steady state and upon the accuracy of the results obtained during the sixth minute. The results of the sixth minute only are included in this report.

An alveolar air sample was obtained in each experiment by means of the Henderson-Haggard trap.[113] This device is operated automatically by the Robinson valve, and collects the last few ml. of terminal expired air of each respiration. At the end of six minutes, this integrated sample was analyzed for oxygen and carbon dioxide in the Haldane apparatus, and the $pACO_2$ was calculated.

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TABLE I.—VENTILATORY DRIVE IN RELATION TO ALVEOLAR AND ARTERIAL pCO_2, ARTERIAL pH AND pO_2

Subject		$pACO_2$	$paCO_2$	pH	paO_2	A-a	O_2V
VSD	3	—	38.0	7.420	35	88	41.2
		—	39.0	7.400	—	—	42.9
		—	38.0	7.420	—	—	43.9
PH	2	28.3	28.0	7.420	93	23	45.1
H	1	31.5	36.0	7.375	76	28	32.1
H	3	—	30.0	7.410	92	23	46.7
		—	30.0	7.400	—	—	45.0
H	8	32.0	33.0	7.443	99	10	35.5
L	1	46.7	46.0	7.410	88	13	24.6
		53.0	60.0	7.351	38	40	23.3
		—	46.0	7.410	—	—	21.9
		39.0	—	7.380	—	—	22.2
		39.4	—	7.445	80	21	26.9
L	2	—	47.0	7.400	67	22	21.8
L	3	46.5	50.0	7.399	51	25	24.5
L	4	44.6	45.0	7.380	67	24	22.7
L	5	29.6	28.0	7.520	75	42	32.8
		33.3	34.0	7.410	80	29	31.2
L	9	31.9	37.0	7.450	55	59	43.9
L	10	36.5	36.0	7.465	—	—	38.3
		32.9	30.0	7.420	87	11	34.7
L	11	27.4	33.0	7.470	42	72	44.3
L	12	31.7	31.0	7.460	89	24	31.6
L	13	—	40.0	7.440	82	19	28.8
		—	42.0	7.410	79	8	27.0
		—	47.0	7.400	93	5	30.8
L	14	52.2	54.0	7.280	85	2	18.5
L	17	—	29.0	7.480	78	38	51.8
		—	29.0	7.500	82	33	61.2
		—	30.0	7.480	65	60	66.9
		25.0	29.0	7.475	—	—	49.9
		19.4	22.0	7.495	37	88	64.0
L	18	32.9	27.0	7.540	95	25	37.3
		32.2	32.0	7.480	91	19	33.6
L	28	—	56.0	7.400	68	23	22.6
L	29	25.9	25.4	7.500	100	21	53.3
L	32	29.0	32.0	7.480	108	13	40.4
P	1	50.0	50.0	7.340	83	2	19.7
P	2	39.5	38.0	7.400	—	—	25.8
P	5	36.2	33.0	7.490	99	12	30.9
P	6	40.3	42.0	7.400	—	—	26.9
X	1	36.0	36.0	7.440	89	15	28.8
M	2	23.9	25.6	7.445	103	18	42.2

An arterial blood sample was collected in 43 experiments simultaneous with the collection of expired and alveolar air as described above. The tension of oxygen and carbon dioxide of these samples was determined immediately after sampling by the Riley bubble technique[169] as modified by Filley;[72] and the pH of the arterial blood was determined directly by use of the Radiometer pH meter in conjunction with the Astrup apparatus.

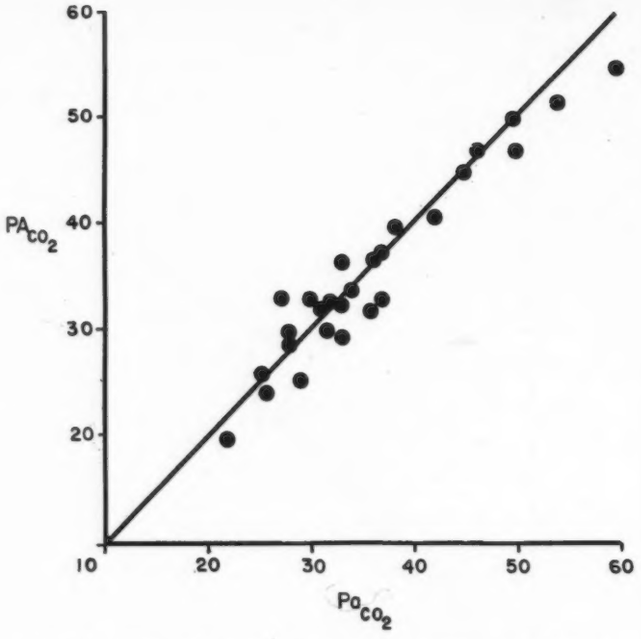

Fig. 2.—Comparison between simultaneous determinations of alveolar and arterial tension of carbon dioxide.

The symbols and abbreviations used here are those adopted by the Federation of American Pulmonary Physiologists (see Appendix).

Throughout the discussion of the results of this investigation the $pACO_2$ is used interchangeably with $paCO_2$. It may be objected that the alveolar CO_2 tensions obtained in the manner described do not represent the true tensions of CO_2 in the arterial blood. This objection raises the problem of the best method of obtaining the alveolar air sample, the question of gas equilibrium between pulmonary capillary blood and the alveoli, and indirectly the old Haldane-Krogh argument over the dead space.[80, 96, 103, 104, 130, 134, 157] The theoretical objections can be answered satisfactorily,[1, 96, 178] but the only method of resolving the question of the accuracy of equating the two is by direct comparison of $pACO_2$ and $paCO_2$. Few simultaneous determinations of both are available in the literature.[60, 61, 73, 82, 133, 180] The Henderson-Haggard trap was employed because alveolar pCO_2 determined by this method has been shown to correlate well with $paCO_2$.[73] In order to check the accuracy of this method in our laboratory, simultaneous determinations of $pACO_2$ and $paCO_2$ were made in 27 experiments in this investigation. The results are listed in Table I and shown in Fig. 2. There are no major discrepancies over the range from 20 to 60 mm. Hg, although individual variations are apparent. These results agree very favourably with those of Dill,[60, 61] Galdston,[82] Lilienthal,[133] Suskind[180] and Filley[73]. It seems reasonable to accept the $pACO_2$ determinations performed by the method described as a fairly accurate reflection of the tension of carbon dioxide in the arterial blood.

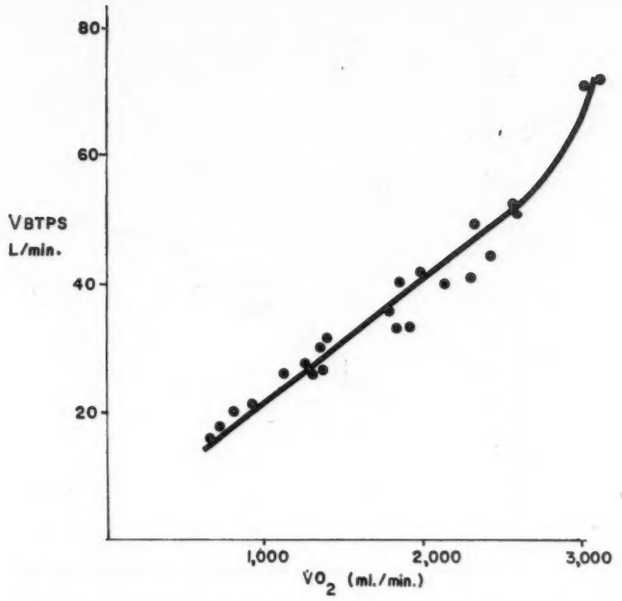

Fig. 3.—The ventilatory response to the stimulus of muscular exercise one normal subject (N2). O_2V = 20.4. r = 0.974.

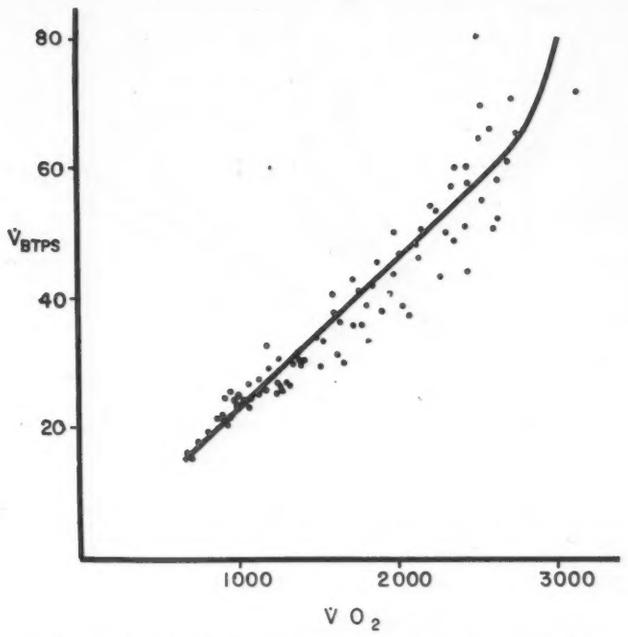

Fig. 4.—Composite graph of the respiratory stimulus-response relationship during exercise in 330 determinations in 17 normal subjects. O_2V = 23.1 ± 3.4. r = 0.896.

RESULTS AND DISCUSSION

The Normal Exercise Stimulus-Response Relationship

Three hundred and thirty observations were made during exercise on 17 normal subjects. The range of exercise was large and varied between 500 and 3000 ml. of oxygen consumption per minute. Despite the great variation in the exercise stimulus, the oxygen ventilation equivalent was remarkably constant in a single individual. Statistical analysis of all the O_2V values showed that the variation between normal individuals was not significant. The normal O_2V calculated from these 330 determinations is 23.1 ± 3.4 litres of air breathed per litre of oxygen consumed. Fig. 3 illustrates the exercise stimulus-response relationship in one normal subject. Similar curves were obtained for the other 16 subjects. The calculated line is straight, except in exhausting exercise where it deviates toward the vertical. If projected, this line will pass through the origin of the graph. Fig. 4 is a composite graph of the results obtained in all experiments on normal subjects. The curve is similar to that obtained for any one subject, but it shows the small variation which occurs in the group.

Figs. 3 and 4 illustrate the precise and proportional increase in pulmonary ventilation which occurs with each increase in the exercise stimulus, except in the extreme range. This observation confirms the impression that there is a linear relationship between pulmonary ventilation and the exercise stimulus over the range from mild to severe exercise. Moreover, the results show that this stimulus-response relationship can be described very simply in normal subjects by calculating the oxygen ventilation equivalent. Since it defines the locus of the curve and expresses the rate of change of the response to the stimulus, the O_2V is an expression of the sensitivity and of the activity of the entire respiratory stimulus-response mechanism in a normal subject at any level of exercise. It is an exact measurement of the respiratory response per unit of oxygen consumed; and although it does not quantitate the activity of the respiratory centre in absolute terms, it is at least an accurate index of that activity during muscular exercise. It may therefore be used to compare the actual respiratory activity with changes in the classical stimuli in normal subjects.

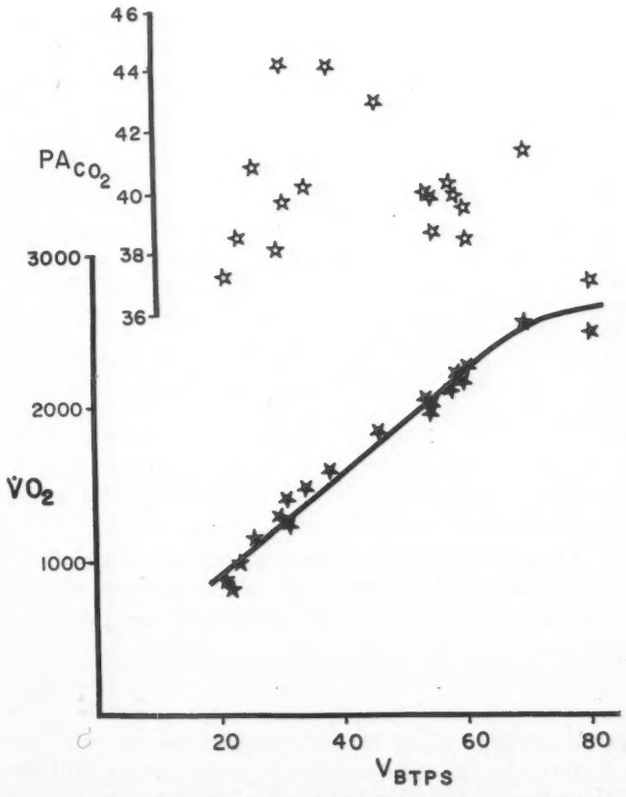

Fig. 5.—The ventilatory response at different levels of exercise in relation to the exercise stimulus, $\dot{V}O_2$ (r = 0.991); and in relation to the classical respiratory stimulus, pCO_2 (r = 0.236). Subject N1.

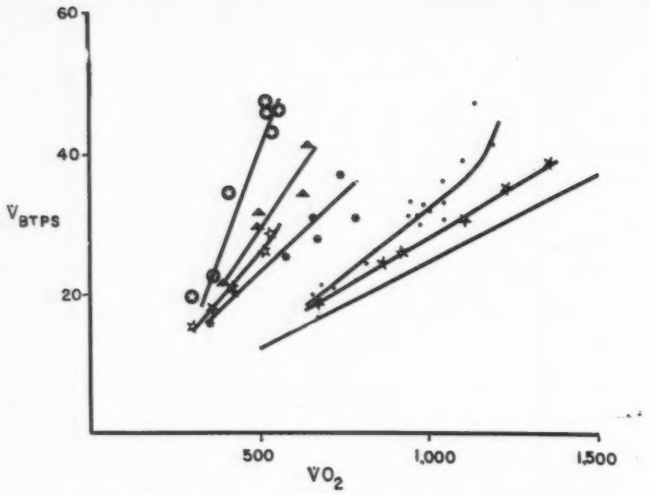

Fig. 6.—The exercise stimulus-response curves in six patients suffering from mitral stenosis. From left to right: M2 (r = 0.820), M61 (r = 0.834), M56 (r = 0.893), M48 (r = 0.782), M1 (r = 0.803) and M4 (r = 0.912). The normal line is shown for reference.

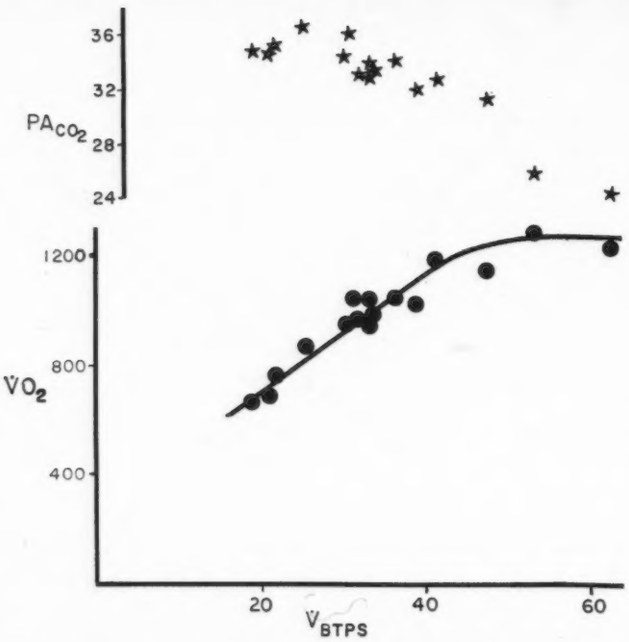

Fig. 7.—The ventilatory response at different levels of exercise in relation to the exercise stimulus, $\dot{V}O_2$ (r = 0.803); and in relation to the classical stimulus, pCO_2 (r = 0.398) in one abnormal subject (M1).

The $pACO_2$ During Exercise in Normal Subjects

The alveolar tension of CO_2 was determined in 215 of these 330 experiments in normal subjects. Although the intensity of the muscular exercise varied from mild to very vigorous, there was little change in pCO_2 in any of the subjects. Statistical analysis of those $pACO_2$ values showed no significant deviation from the mean in the whole group and no consistent trend in any individual. This observation confirms those of others.[12, 17, 101, 126, 133, 150] Statistical analysis of the $pACO_2$ determinations in relation to the oxygen consumption and in relation to the minute ventilation showed no correlation either between $pACO_2$ and $\dot{V}O_2$ or between $pACO_2$ and $\dot{V}_{BTPS}$. Fig. 5 is a typical illustration of the contrast between pCO_2 and work as stimulants of pulmonary ventilation in a single subject. There is a very significant correlation between the exercise stimulus and pulmonary ventilation (r = 0.991), while that between pCO_2 and pulmonary ventilation is not significant (r = 0.236). Since there is no correlation between $pACO_2$ and either the work stimulus or the respiratory response, it is difficult to accept the hypothesis that pCO_2 directly regulates these rather precise exercise stimulus-response curves. The respiratory centre responds in an orderly and predictable way to each increase in the work stimulus, regardless of the small and inconsistent change in pCO_2.

The Exercise Stimulus-Response Relationship in Abnormal Subjects

Three hundred and seventy similar observations were made on 67 patients suffering from heart disease, and 81 observations on 32 patients with pulmonary disease. The determinations of oxygen ventilation equivalent showed that there was a wide variation in respiratory activity among those patients. The ventilatory activity ranged from normal to more than double the normal respiratory response to exercise. However, the O_2V was remarkably constant in each subject regardless of the level of exercise. Fig. 6 is an illustration of the stimulus-response curves obtained in six of these subjects, and similar curves are obtained for the other patients. The normal line is shown for reference. These stimulus-response curves are straight, and if projected they will pass through or near the origin of the graph. The respiratory response of these abnormal subjects is proportional to the exercise stimulus, and this proportionality is maintained in each subject at different levels of exercise, despite the degree of hyperventilation. It follows that the individual O_2V, although it varies between subjects, is an accurate expression of the slope of a subject's stimulus-response curve. It is therefore a quantitative expression of the respiratory activity of these patients. It seems reasonable to accept the O_2V of these patients as a parameter which may be used to compare their respiratory activity with changes in the classical stimuli.

The $pACO_2$ in These Patients

The $pACO_2$ determinations in these patients varied from approximately 20 to 60 mm. Hg. However, there was little variation in $pACO_2$ in a single subject regardless of the level of exercise, and there was no correlation between $pACO_2$ and either the work stimulus or the respiratory response. In this respect these subjects are similar to the normal. Fig. 7 is an illustration of the contrast between pCO_2 and work as respiratory stimuli in one of those subjects (M1); similar graphs are obtained for the other 98 patients. As in the normal subject, the correlation between pCO_2 and pulmonary ventilation is not statistically significant (r = 0.398). In contrast the correlation between the exercise stimulus and the ventilatory response is highly significant (r = 0.803). These results are similar to those shown in Fig. 5 in the normal subject. It should be emphasized, however,

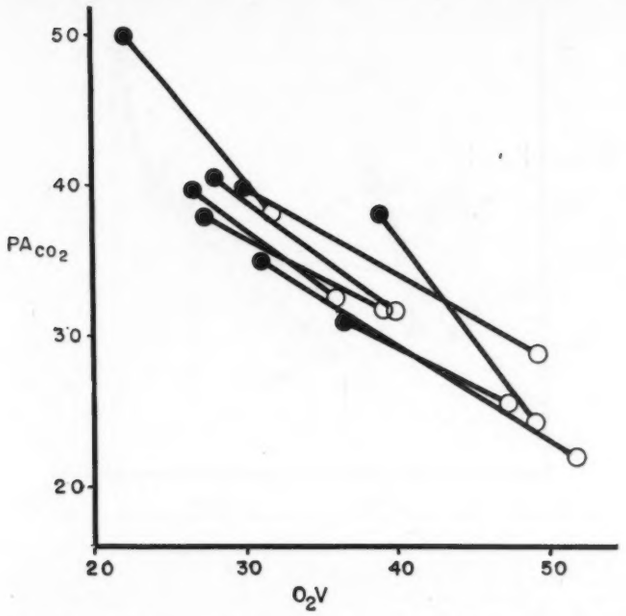

Fig. 8.—The relationship between respiratory activity (O_2V) and the classical respiratory stimulus, pCO_2, during exercise before and after commissurotomy in 8 patients suffering from mitral stenosis (M3, M26, M31, M51, M54, M56, M62 and M64). The preoperative determinations are shown as open circles and the postoperative as closed circles.

that the pulmonary ventilation per unit of work (O_2V), which is high in the majority of these patients, demonstrates a degree of hyperventilation despite the fact that the corresponding $pACO_2$ is invariably less than normal. Both the lack of correlation between pCO_2 and pulmonary ventilation, and the fact that hyperventilation is present despite a low pCO_2, make it difficult to accept the thesis that pCO_2 is regulating these precise respiratory responses to increases in muscular exercise in these patients.

Twenty-three patients who were suffering from mitral stenosis were investigated after, as well as before, mitral commissurotomy. It was observed that the O_2V had decreased in 14 of them after operation. This fall in pulmonary ventilation occurred despite a corresponding increase in pCO_2. This phenomenon is shown in Fig. 8 in 8 of these subjects. Although the volume of pulmonary ventilation per unit of work (O_2V) is less after successful mitral commissurotomy,

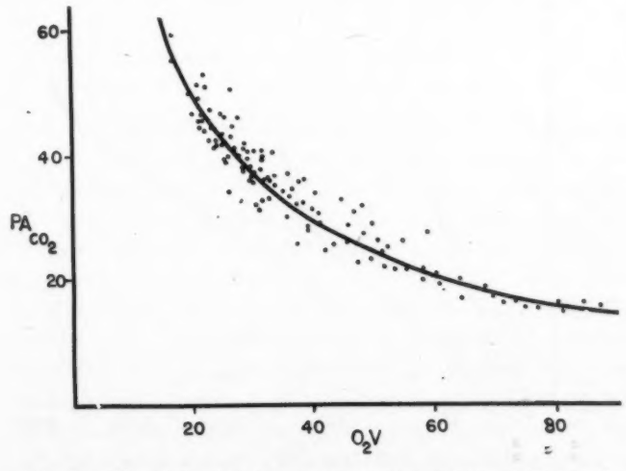

Fig. 9.—The relationship between respiratory activity (O_2V) and the classical respiratory stimulus, pCO_2, during exercise in 454 determinations on 151 subjects. r = 0.954.

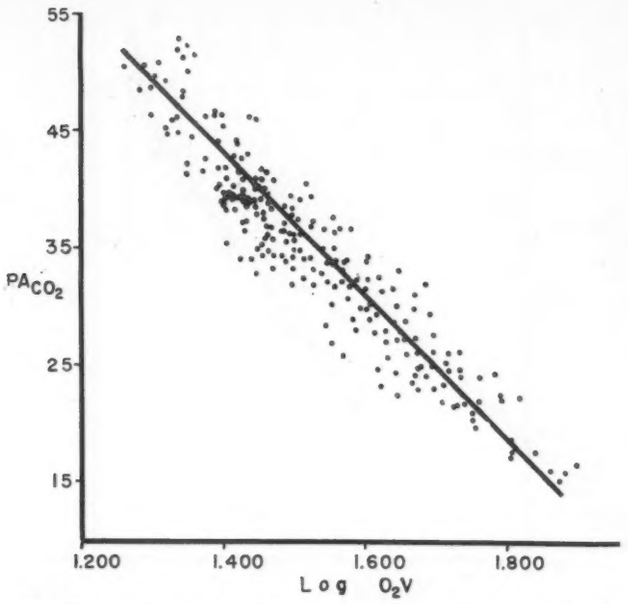

Fig. 10.—Semilogarithmic plot of the data illustrated in Fig. 9. r = 0.954

the corresponding tension of CO_2 is greater. This observation is again incompatible with the hypothesis that CO_2 plays an effective role in the control of pulmonary ventilation in such patients.

Indeed, the results obtained in the investigation of patients with cardiac and pulmonary disease suggest that, instead of a postulated positive correlation between respiratory activity (O_2V) and pCO_2, there actually exists an inverse relationship between these parameters. Fig. 9 is a plot of all determinations of O_2V and $pACO_2$ obtained in this investigation in all subjects, both normal and abnormal. Fig. 10 is a semi-logarithmic plot of the same data. It is evident that $pACO_2$ is a negative exponential function of respiratory activity; as the O_2V is increased, the $pACO_2$ decreases. The large number of experiments, the number of subjects, the range of pathological material and the excellent correlation coefficient (-0.954) of this curve all suggest that this is not a fortuitous relationship. Moreover, the same phenomenon has been demonstrated in single subjects (Fig. 8). It seems impossible to reconcile this observation with the classical theory of control of pulmonary ventilation. The more probable explanation is that this graph is a demonstration of a "rinse-out" phenomenon; as the respiratory activity is increased by some stimulus, at present unknown, CO_2 is washed out of the blood. The pCO_2 is dependent upon the activity of the respiratory centre and does not regulate it as the classical theory maintains.

The Ventilatory Response to Exercise in Relation to the Sensitivity of the Respiratory Centre to CO_2

Normal individuals adapt to a low $paCO_2$ at high altitude,[92, 161] and the respiratory centre accommodates itself to a high pCO_2 in certain pathological conditions.[144, 174, 180] A change in the sensitivity of the respiratory centre to inspired CO_2 has sometimes accompanied the change in $paCO_2$ under these con-

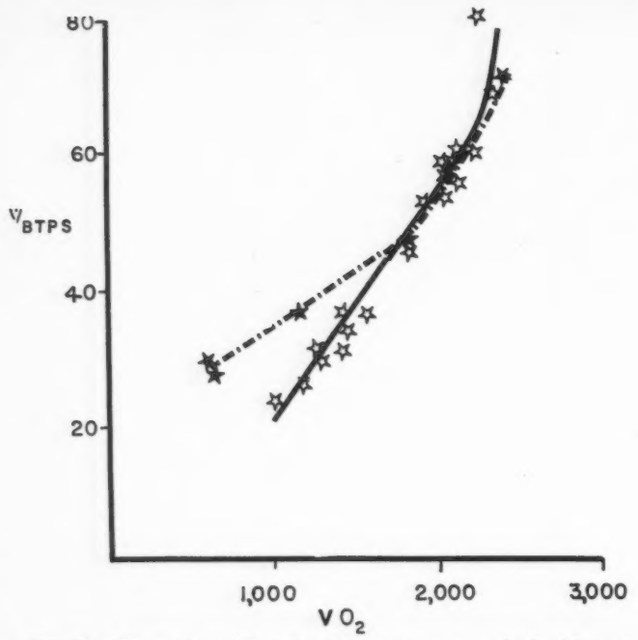

Fig. 11.—Illustration of the stimulus-response curves obtained in one normal subject (N1) during exercise of different degrees of intensity, while he was breathing air (solid line) and 2.16% CO_2 in air (broken line).

ditions in resting subjects. This observation has been advanced as support for the hypothesis that the sensitivity of the respiratory centre to $paCO_2$ increases during increasing exercise.[12] If this hypothesis is correct, then the increased sensitivity to pCO_2 should be demonstrable when subjects breathe a constant concentration of CO_2 during increasing levels of exercise. One would expect to obtain a stimulus-response curve with an increased slope located above the usual curve obtained when the subject breathes air.

The contrast between the ventilatory response of a normal subject at various levels of exercise to 2% CO_2 in air, and that obtained when breathing air alone during exercise, is shown in Fig. 11. In the low

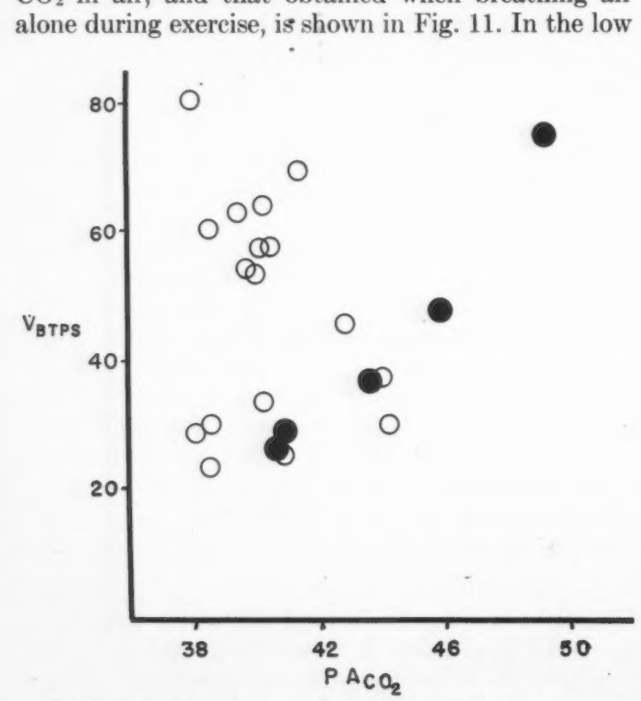

Fig. 12.—The classical stimulus, pCO_2, in relation to the minute ventilation at different levels of exercise in one normal subject (N1), while he was breathing air (open circles) and 2.16% CO_2 in air (closed circles).

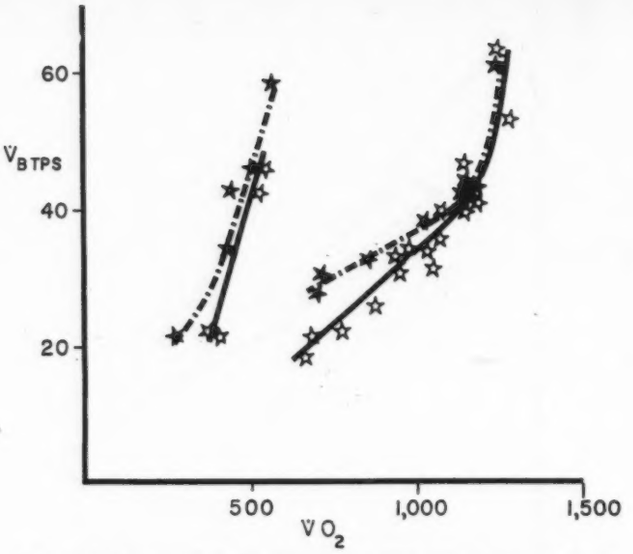

Fig. 13.—Illustration of the stimulus-response curves obtained in two abnormal subjects (M2 and M1) during exercise of different degrees of intensity, while they were breathing air (solid lines) and 2.16% CO_2 in air (broken lines).

ranges of exercise, the increased ventilation caused by CO_2 is quite apparent. As the exercise stimulus is increased, however, the effect of the inspired CO_2 upon ventilation gradually diminishes until at an exercise stimulus equivalent to approximately 1800 ml. $\dot{V}O_2$, this concentration of CO_2 has no effect at all. The corresponding $pACO_2$ values are shown in Fig. 12. The inspired CO_2 is responsible for an increase in $pACO_2$ of approximately 10 mm. Hg at a pulmonary ventilation of 80 litres per minute; despite this increase, the ventilation under both conditions is the same.

The respiratory response of two abnormal subjects (M1 and M2) to 2% CO_2 in air during increasing levels of exercise is shown in Fig. 13. One of these subjects had a moderately elevated, and the other an extremely high, respiratory activity, as quantitated by means of the oxygen ventilation equivalent. The CO_2 curves deviate toward, and merge with, the air-breathing curves as in the normal subject. The junction of these curves occurs, however, at a much lower exercise stimulus in these two patients. Fig. 14

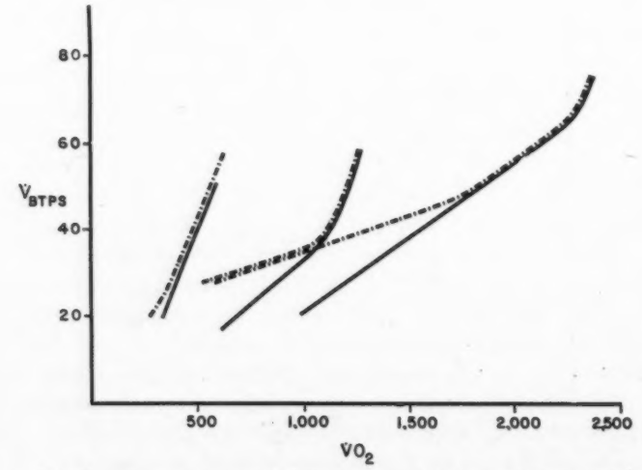

Fig. 14.—A comparison of the stimulus-response curves obtained in the two abnormal subjects (Fig. 13) with that of the normal (Fig. 11). Solid lines were obtained in air, and the broken lines on 2.16% CO_2 in air.

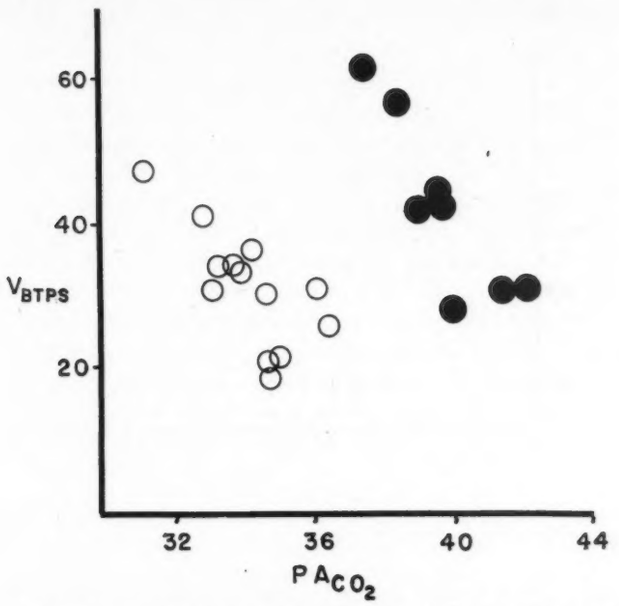

Fig. 15.—The pCO_2 in relation to the minute ventilation at different levels of exercise in abnormal subject M1, while he was breathing air (open circles) and 2.16% CO_2 in air (closed circles).

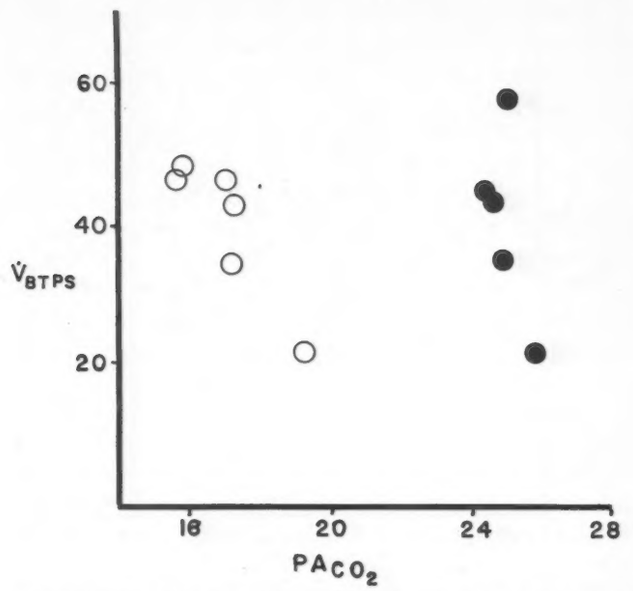

Fig. 16.—The pCO_2 in relation to the minute ventilation at different levels of exercise in abnormal subject M2, while he was breathing air (open circles) and 2.16% CO_2 in air (closed circles).

illustrates the difference between the normal and the two abnormal subjects. The sensitivity of the respiratory centres of the two abnormal subjects to CO_2 is much less than the normal, and it is least in the subject with the higher respiratory activity. In all three, there is a decreasing, not an increasing, sensitivity to CO_2 as the exercise stimulus is increased. Figs. 15 and 16 show the corresponding increases in $pACO_2$ in these two abnormal subjects during exercise; the increase in $pACO_2$ is proportionately much greater than in the normal subject (Fig. 12), but the ventilatory effect has been much less.

These findings demonstrate that there is a decreasing sensitivity to CO_2 as exercise is increased in both normal and abnormal subjects. The sensitivity to CO_2 is less than normal in subjects who hyperventilate during exercise. With increasing exercise the ventilatory effect of CO_2 decreases in these patients also, despite a proportionately greater increase in pCO_2. This appears to be a conclusive demonstration that the "increasing sensitivity" hypothesis is untenable.

The Pulmonary Ventilation During Muscular Exercise in Relation to the pCO_2

It is difficult to reconcile any of the foregoing results with the hypothesis that the arterial tension of carbon dioxide plays a determining role in the control of pulmonary ventilation during muscular exercise. There is little or no change in pCO_2 during exercise in any subject, regardless of the degree of muscular activity. The data presented here demonstrate that this observation is true of abnormal subjects as well as normal. The correlation between pCO_2 and pulmonary ventilation in each of these 151 subjects is not significant despite a remarkably precise proportionality between the exercise stimulus and the respiratory response. This observation is in contrast to the artificial increase in pCO_2 which is necessary in order to stimulate an increase in pulmonary ventilation in resting subjects. The pCO_2 is below normal in subjects who hyperventilate, and the decrease in pCO_2 seems to be approximately proportional to the degree of hyperventilation. The pCO_2 has been shown to be a negative exponential function of respiratory activity. Instead of regulating the activity of the respiratory centre during muscular exercise, the pCO_2 seems to be determined by the respiratory drive of the individual. No other interpretation seems adequate to explain these results.

An attempt to reconcile some of these discrepancies in the classical theory by invoking a possible change in sensitivity of the respiratory centre to CO_2 during exercise has served only to emphasize the inadequacy of the theory. Both normal and abnormal subjects show a decreasing sensitivity to CO_2 as the exercise stimulus is increased. Moreover, those subjects who hyperventilate are less sensitive to CO_2 than the

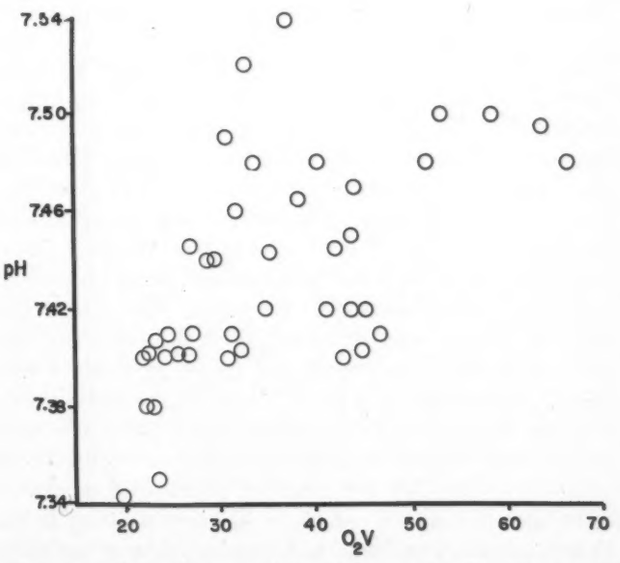

Fig. 17.—The respiratory activity ($\dot{O}_2V$) and the pH of the arterial blood during exercise on 43 occasions in 27 subjects.

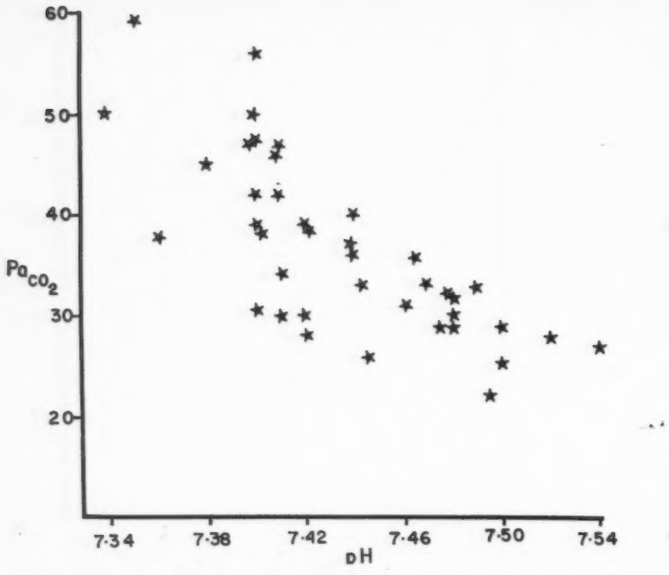

Fig. 18.—The relationship between simultaneous determinations of the pH of the arterial blood and $paCO_2$ during exercise on 40 occasions in 25 subjects.

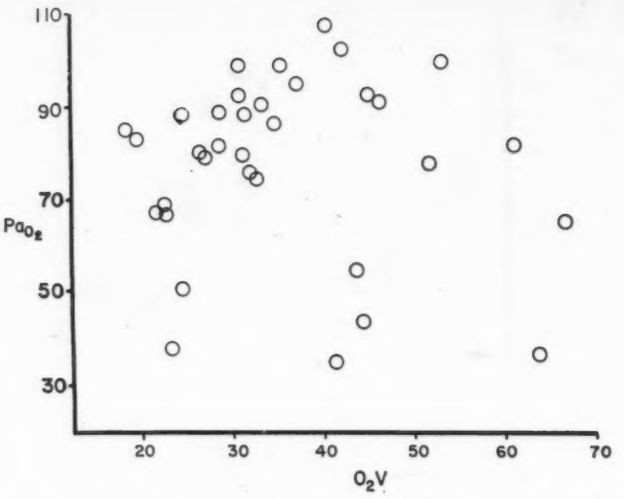

Fig. 19.—The respiratory activity (O_2V) and the arterial pO_2 on 34 occasions during exercise in 25 subjects.

normal subject, despite a relatively greater increase in their pCO_2 when carbon dioxide in air is inspired.

One must conclude that some other more powerful factor or factors, at present unknown, are acting through the respiratory centre in response to the physiological stimulus of exercise to cause hyperpnea proportional to the exercise stimulus. The arterial tension of CO_2 seems to be determined by this mechanism during exercise in both normal and abnormal subjects. The logical conclusion is that the role of CO_2 in the control of the hyperpnea of muscular exercise in both normal and abnormal subjects must be a minor one, if indeed it plays any role in this physiological state.

THE RELATIONSHIP OF RESPIRATORY ACTIVITY TO THE OTHER TWO CLASSICAL STIMULI

The pH of the Arterial Blood

The data available in the literature reveal that the change in the pH of the arterial blood is small, when it occurs at all, during muscular exercise in normal subjects.[11, 27, 43, 52, 105, 139, 140, 149, 154] Moreover, Comroe has shown that the direct effect on the respiratory centre of a change in pH is negligible. Nevertheless, this small change in the pH of the arterial blood, if and when it occurs during muscular exercise, has been invoked to explain some of the inadequacy of the role of pCO_2.[11, 83, 84, 91, 95, 188] One might expect, therefore, to be able to demonstrate some degree of acidemia during muscular exercise. The pH of the arterial blood was determined in 43 experiments in 27 subjects. The results are listed in Table I and shown graphically in Fig. 17. None of the individuals who have a high respiratory activity are acidotic, and the general tendency is towards a greater degree of alkalosis as the O_2V is increased. Simultaneous determinations of pH and $paCO_2$ in 40 experiments (Table I) are compared in Fig. 18. A low $paCO_2$ is invariably associated with alkalosis during exercise. The $paCO_2$ not only is below normal in many patients who have an increased respiratory activity (Fig. 9), but it decreases still further during exercise in response to some unknown stimulus. The result is an alkalosis, the degree of which seems to depend upon the individual's respiratory activity. It is not possible on the basis of these results to establish pH as an effective respiratory regulator during muscular exercise. The pH of the arterial blood will not explain either hyperpnea or hyperventilation. The role of pH in the control of pulmonary ventilation, like that of pCO_2, during muscular exercise is a passive one. It seems to be determined by whatever mechanism is driving the respiratory centre.

The Arterial pO_2

A low paO_2 has been invoked to explain the hyperventilation of patients with cardiac and pulmonary disease,[25, 48] and hypoxia is said to be the cause of the hyperventilation observed during exhausting exercise in both normal and abnormal subjects. The phenomenon of hyperventilation in normal subjects during exhausting exercise is shown in Figs. 1, 3 and 4. The respiratory stimulus-response curves deviate towards the vertical axis at high oxygen consumption. This has been ascribed to the "acidosis of exhaustion" in normal subjects,[95] or to hypoxia in both normal[12, 47] and abnormal[48] subjects. The evidence cited for acidosis as a cause is the observation that lactic acid accumulates when the blood supply of the exercising muscles is inadequate.[27, 43, 95, 105, 147, 149, 154] The hypothesis of hypoxia as a cause has as its basis the fact that the increase in hyperpnea can be relieved by increasing the concentration of inspired oxygen.[13, 48, 120, 121] Considerable doubt has been cast on both hypotheses recently by Mitchell,[146] who showed that the paO_2 did not decrease in normal subjects during exhausting exercise and that the change in pH was not significant. Moreover, it has been shown that the arterial pO_2 must fall below 65 mm. Hg before any significant increase in pulmonary ventilation occurs, and even below that threshold the rate of increase is small.[92, 95]

The paO_2 was determined on 34 occasions during exercise in 25 of the subjects in this investigation in order to check the possibility that it might be a contributory factor in the control of the hyperpnea and hyperventilation observed. The results are listed in Table I. Fig. 19 shows the relationship between paO_2 and respiratory activity (O_2V) in those subjects. The paO_2 is below 65 mm. Hg, in only six subjects, and two of the six did not hyperventilate despite the low pO_2. Moreover, there is no correlation at all between respiratory activity and the arterial tension of oxygen in those subjects. These results cannot be reconciled with the hypothesis that hypoxia is a factor to be considered in the control of the respiratory response to exercise in these subjects.

CONCLUSION

There is a large volume of evidence which demonstrates conclusively that carbon dioxide is a powerful respiratory stimulant; and there is indisputable proof that the arterial tension of oxygen and the pH of the arterial blood do have some effect on respiration. The role of these three classical stimuli in the control of pulmonary ventilation has been investigated and it has been found that they are not an adequate explanation either for the hyperpnea of muscular exercise in normal and abnormal subjects, or for the hyperventilation observed in patients suffering from cardiopulmonary disease. It seems that they play a minor role, if any, in the control of pulmonary ventilation under normal conditions. The results demonstrate that the pCO_2 is determined by the activity of the respiratory centre. There is no correlation between pCO_2 and pulmonary ventilation at various levels of exercise in any of our subjects. Patients who hyperventilate have a low pCO_2, and these subjects are less sensitive to inspired CO_2 than is the normal, despite the low pCO_2. Both normal and abnormal subjects show a decreasing sensitivity to CO_2 as the exercise stimulus is increased. These observations are not compatible with the hypothesis that CO_2 is an effective regulator of the respiratory response to muscular exercise. A possible change in the pH of the arterial blood cannot be invoked to explain the inadequacy of carbon dioxide. Significant acidemia was not found in any subject; and the results show that alkalosis is usually present during exercise in subjects who hyperventilate. The paO_2 may be dismissed as a factor in normal subjects;[146] the results suggest that it is of little importance as a cause of hyperventilation in patients with cardiopulmonary disease.

This has been a clinical investigation in which changes in the classical stimuli have been compared to a mathematical quantitation of the activity of the respiratory centre (O_2V) of normal and abnormal subjects during muscular exercise in the steady state. This approach to the study of physiology has much to offer. It is not possible to induce changes in organs in human subjects, but it is possible to study the effect of pathological changes in organs upon various systems.

Investigations of this type are being conducted every day in hospitals; and such studies are capable of contributing to our knowledge of normal physiology. It must be recognized, however, that this sort of investigation derives its efficacy from a study of the difference between individuals. In this respect, it may be said that the 151 subjects of this investigation are representative of a wide variation in cardiopulmonary status. The large number of experiments, and the rather precise stimulus-response curves shown, considered in relation to the number of subjects, make it extremely unlikely that the results obtained are fortuitous.

No effort has been made in this investigation to identify any factors which may control or influence pulmonary ventilation during muscular exercise, although it is possible that a similar approach could be utilized to that end. Attention has been directed to an assessment of the role of the classical stimuli in the control of hyperpnea and hyperventilation during muscular exercise. The problem of identifying the factors which control pulmonary ventilation has not been solved. The classical theory is not an adequate hypothesis. The role of $paCO_2$, paO_2 and arterial pH in the control of pulmonary ventilation will have to be reconsidered. A new approach to the problem of identifying the factor or factors which control the activity of the respiratory centre under physiological conditions is probably necessary.

During the past 30 years, the emphasis in the study of respiratory physiology has been upon the humoral factors which are known to influence respiration. In recent years, some attention is being given to the possibility that neural factors may be at least as important.[7, 10, 55, 156] There are many phenomena in respiratory physiology which are explainable only by invoking some nervous mechanism. Among these phenomena are: the initiation of hyperpnea when exercise is begun; the relief obtained by breathing an inert gas after breath-holding in expiration; and the hyperventilation observed in acute anemia, cardiac disease, pulmonary embolism, pulmonary hypertension and other pathological states. Although it seems evident that these neural factors must exist, they have not been identified. There may be other unknown neural, and possibly humoral, factors which influence the respiratory response to exercise. It may be that the activity of the respiratory centre is dependent upon an integration of many factors, an opinion held by many physiologists. It is also possible that the respiratory centre is controlled during muscular exercise by one mechanism which has not been discovered. In this regard, the possibility that nervous reflexes arising in the heart and lungs may play a dominant role in controlling pulmonary ventilation during exercise requires further investigation. In particular, the effects on respiration of changes in cardiac output and of stimulation of possible pressoreceptors in the pulmonary vasculature are not at all clear. It is possible that the attention which is now being directed to the physiology of the pulmonary circulation[7, 10, 31, 67–71, 79, 151,

[152, 155, 156, 162, 164, 171, 178] may provide some of the answers to this perplexing problem.

APPENDIX

List of Abbreviations Used

V = gas volume
$\dot{V}$ = gas volume per unit of time
P = gas pressure
F = fractional concentration of dry gas
R = respiratory exchange ratio
I = inspired gas
E = expired gas
A = alveolar gas
STPD = 0°C., 760 mm. Hg, dry
BTPS = body temperature, ambient pressure, saturated
a = arterial blood

These symbols can be combined to express any desired relationship, for example,

$\dot{V}O_2$ = oxygen consumption per minute
$paCO_2$ = pressure of carbon dioxide in the arterial blood

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USE OF LOCAL INJECTIONS OF CORTICOSTEROIDS INTO CUTANEOUS LESIONS

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THE ANTI-INFLAMMATORY effect of corticosteroids, injected locally into cutaneous lesions, has been studied by a number of investigators.[1-4] Favourable results have been reported from the local use of hydrocortisone and recently from the use of topical injections of triamcinolone.[5, 6]

MATERIALS AND METHOD

Aqueous suspensions of the following preparations were used and their effects compared:

Hydrocortisone acetate	25 mg. per c.c.
6-methylprednisolone acetate with carbowax (Depo-Medrol*)	25 mg. per c.c.
6-methylprednisolone acetate with carbowax (Depo-Medrol*)	40 mg. per c.c.

For each subcutaneous injection 0.05 to 0.1 c.c. of the above materials was used, and lesions of comparable size and duration were chosen. Two hundred and eight patients were treated and followed up: 155 had acne vulgaris, 12 sebaceous cysts, 10 discoid lupus erythematosus, 10 alopecia areata, seven lichen planus, four neurodermatitis, three psoriasis, two keloids, two granuloma annulare and three hydradenitis.

TREATMENT AND RESULTS

The patients with acne vulgaris were divided into four groups for comparison.

Group 1.—Seventy-nine patients, adolescents and young adults, with superficial pustular lesions were given identical amounts of the different steroid preparations (0.05 to 0.1 c.c.) into different lesions of the same size, present for approximately the same period of time. Results were as follows:

TABLE I.—SUPERFICIAL PUSTULAR LESIONS: TREATMENT AND RESULTS

Preparation	*Dose*	*Average healing time of lesions*
Hydrocortisone	1 - 2.5 mg.	66 hours, with residual erythema
6-methylprednisolone	1 - 2.5 mg.	48 hours, " " "
6-methylprednisolone	2 - 4 mg.	24 hours, " " "
Untreated control	-	144 hours, " " "

Group 2.—Twenty patients with deep pustular acne were given one injection of 0.05 to 0.1 c.c. of each steroid into respective lesions of approximately the same size and duration. Results were:

TABLE II.—DEEP PUSTULAR ACNE: TREATMENT AND RESULTS

Preparation	*Dose*	*Average healing time of lesions*
Hydrocortisone	2.5 mg.	5 days
6-methylprednisolone	2.5 mg.	4 "
6-methylprednisolone	4.0 mg.	3 "
Untreated control	-	8 to 14 days

*Depo-Medrol donated by the Upjohn Company Limited.

Group 3.—In this group of 22 patients with simple cystic acne, an average of two injections of 2 to 4 mg. of 6-methylprednisolone in wax (Depo-Medrol, 40 mg./c.c.) was sufficient to produce clearing of the cyst without subsequent relapses, while an average of four to six injections was necessary with the weaker 6-methylprednisolone in wax (Depo-Medrol) solution to achieve the same results. Hydrocortisone was even less effective and relapses occurred.

The following case report illustrates a typical response. A female patient, aged 29, had severe cystic acne for nine years. Routine acne therapy cleared the condition to some extent, but large cysts appeared from time to time, particularly premenstrually, regressing to some degree after menstruation and increasing in size after ovulation. Three such cysts, showing inflammatory activity of equal size and duration (three months), were treated for comparative purposes: 2.5 mg. of hydrocortisone, 2.5 mg. of the diluted 6-methylprednisolone and 4 mg. of the undiluted 6-methylprednisolone were injected into the respective cysts. Results are shown in Table III. This patient was followed up for more than six months during which time no relapse in any of the lesions occurred.

Group 4 consisted of 34 cases of chronic cystic acne with multiple and conglobated cysts. These patients showed a variable response to local steroid injections, thus making tabulation of averages impractical. Some responded to one or two injections of 6-methylprednisolone in wax, while others required months of treatment. Hydrocortisone either was not effective or a very considerable number of injections was required. Diluted 6-methylprednisolone had an intermediate effect.

Chronic Cystic Lesions

This group of patients had chronic cystic lesions on the scalp, face and ears and retroauricularly. The majority, if not all, of these cysts were of sebaceous type, but dermoid cysts may have been included, as no biopsies were taken. These lesions had been present for a long period of time, in four instances for many years. Two to four injections of 6-methylprednisolone resulted in resorption of the cyst, and no relapses occurred during the six-month follow-up period in every case. Hydrocortisone was not as effective; some regression occurred but the cysts tended to relapse.

Discoid lupus erythematosus

This group of 10 patients had been previously treated with chloroquine or diiodochloroquine or combinations of these drugs for a long time, but had been only partially controlled. In all instances complete clearing of the treated areas was achieved with one to three injections of 6-methylprednisolone. 6-Methylprednisolone was markedly superior to hydrocortisone, particularly with regard to relapses. This was well demonstrated in one patient who had

TABLE III.—TREATMENT AND RESULTS IN AN ILLUSTRATIVE CASE OF CYSTIC ACNE

Date	*One cystic lesion treated by hydrocortisone (25 mg./c.c.)*	*One cystic lesion treated by 6-methylprednisolone in wax (25 mg./c.c.)*	*One cystic lestion treated by 6-methylprednisolone in wax (40 mg./c.c.)*
January 4	2.5 mg. (0.1 c.c.) injected.	2.5 mg. (0.1 c.c.) injected.	4 mg. (0.1 c.c.) injected.
January 15	Lesion flatter. Injection of 2.5 mg. repeated.	Lesion somewhat flatter and smaller. Injection of 2.5 mg. repeated.	Lesion disappeared but slight depression left. No therapy required.
January 21	Acne quiescent, but lesion palpable. Injection of 2.5 mg. repeated.	Lesion smaller but palpable. Injection of 2.0 mg. repeated.	No trace of lesion.
February 4	Marked exacerbation of lesion premenstrually. Injection of 2.5 mg. repeated.	Very slight activity in lesion. Injection of 2.0 mg. repeated.	
February 11	Lessened activity in lesion, but still palpable. Injection of 2.5 mg. repeated.	Lesion very small but palpable. Injection of 1.0 mg. given.	
March 3	Further premenstrual flare-up of lesion. Hydrocortisone discontinued. 6-Methylprednisolone, 4.0 mg., injected.	Lesion disappeared, but slight depression left.	
March 25	Lesion disappeared, but slight depression left.	No trace of lesion.	

been treated with both steroids in different areas. While all plaques disappeared after treatment, exposure to sun resulted in relapse in the hydrocortisone-treated areas, while sites treated by 6-methylprednisolone remained inactive.

Alopecia Areata

Local regrowth of hair was induced regularly by injections of 6-methylprednisolone in circumscribed areas of alopecia areata. Hair growth was more quickly achieved and more marked in lesions injected with 6-methylprednisolone than in those treated with hydrocortisone.

Lichen Planus

Local injections of steroids are useful in discrete hypertrophic lesions of lichen planus, and one or two injections of 6-methylprednisolone proved more effective than four to five injections of hydrocortisone acetate.

Neurodermatitis

Circumscribed areas of lichenified neurodermatitis or of lichen simplex responded satisfactorily to this form of treatment. Pruritus subsided almost immediately and healing occurred after one treatment with 6-methylprednisolone in divided doses into the plaques, while it took four to five injections of hydrocortisone to achieve the same results.

Psoriasis

In solitary and circumscribed psoriatic plaques, regression was achieved with one to two injections of 6-methylprednisolone in divided doses.

Hydradenitis

With local injection of 6-methylprednisolone into small nodules and large deep-seated, bluish-red axillary masses of sweat gland abscesses, rapid absorption of lesions was achieved with one or two injections. In one case only, 10 mg. of kanamycin (Kantrex) was injected with the steroid.

Keloids

Keloids showing flattening and "pulling" of the scar subsided after one to three injections of 6-methylprednisolone. The cosmetic result was equivocal.

Granuloma Annularis

This lesion responded to injection of all of these steroid preparations.

Dupuytren's Contracture

In the one case treated, marked softening and increased motility were observed after three injections of 6-methylprednisolone, 8 mg. in divided doses.

DISCUSSION

These investigations were carried out to compare the efficacy of three preparations of steroids.

In all instances, the high concentration of 6-methylprednisolone in wax (Depo-Medrol, 40 mg./c.c.) was more effective than the weaker concentration (25 mg./c.c.) of the same preparation, which in turn was more effective than the hydrocortisone (25 mg./c.c.).

Treatment of pustular acne by this method is indicated only in the occasional case, for cosmetic reasons. In cystic acne, on the other hand, it appears to be the most effective method of local therapy, as it is also for sebaceous cysts, where one or two injections may obviate the necessity of surgical intervention. However, with conglobated cysts, less effect was observed, probably owing to a low concentration of steroid in the interconnecting spaces.

This form of therapy is also of practical value in the control of lesions of chronic lupus erythematosus. In hypertrophic lichen planus, a disorder notoriously resistant to therapy, and in occasional cases of chronic lichenified neurodermatitis, the results were good and the immediate cessation of pruritus was particularly satisfactory. This method is also practical in the treatment of solitary, small

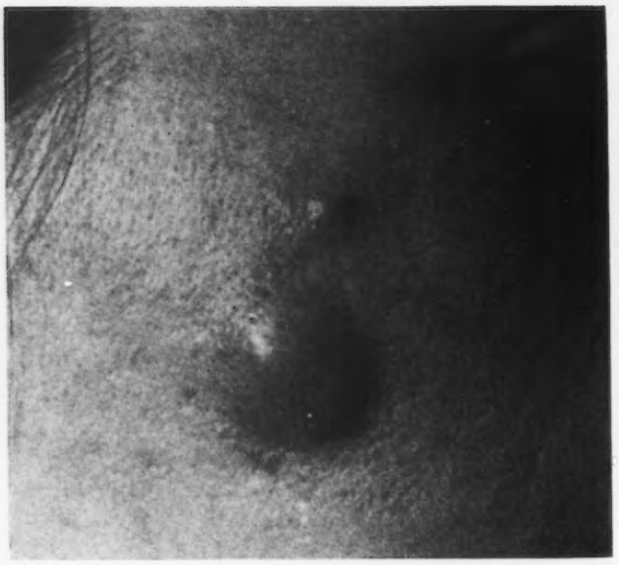

Fig. 1.—Cyst on right cheek before treatment with 0.1 c.c. of 6-methylprednisolone in wax (40 mg./c.c.).

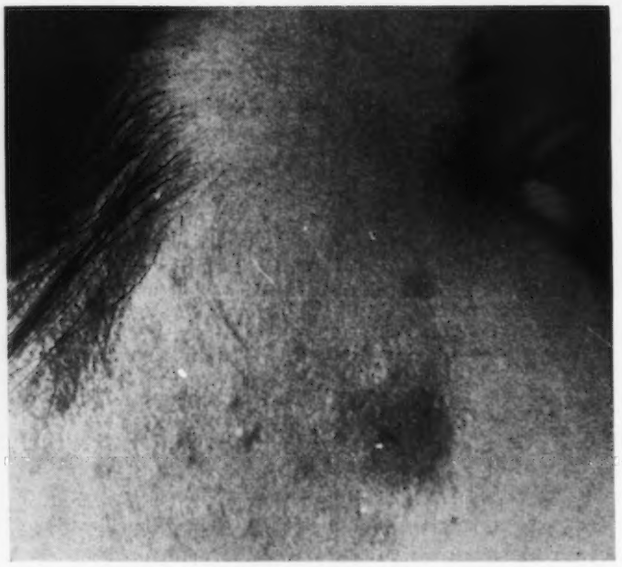

Fig. 2.—Same cyst 11 days after single injection of 6-methylprednisolone in wax.

lesions of alopecia areata and of single psoriatic plaques, but could not be used in large areas, as the procedure would be too slow, painful and expensive. In alopecia areata, 40 mg. of 6-methylprednisolone, intramuscularly, twice a week for four weeks, 20 mg. twice a week for a further four weeks, and then 20 mg. once a week for two weeks followed by a very small maintenance dose orally, was more successful.

In psoriasis vulgaris, steroid therapy in any form gave unsatisfactory results in long-term observations, and we have discontinued its use.

Fig. 3

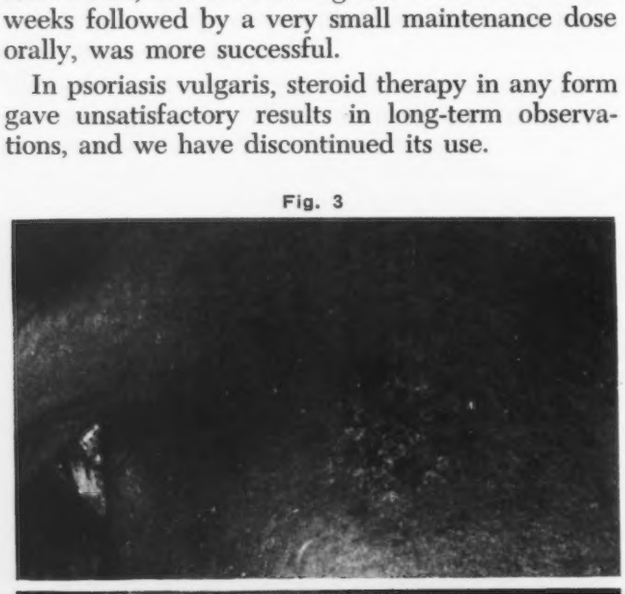

Fig. 4

Fig. 3.—Relapsing lupus erythematosus before injection therapy. Fig. 4.—Three weeks after injection of 8 mg. of 6-methylprednisolone in wax in divided doses. No relapse occurred in a nine-month follow-up period.

No systemic effects were observed in this series using local intradermal injections. The total intradermal dosage of combined steroids never surpassed 40 mg. and was considerably lower in most instances. A temporary superficial atrophy occurred in the majority of cases. The skin on the forehead and the nape of the neck appears to be particularly prone to develop a slight depression, which usually disappeared after two months. A small discoloration *in situ* due to a deposit of the 6-methylprednisolone was also frequently observed; this usually disappeared in a short period of time. More marked atrophy occurred in conditions in which an inflammatory infiltration was resorbed, and the permanent atrophy seen in some cases of lupus erythematosus was attributed to the underlying disease rather than to the steroid injection.

SUMMARY

Two hundred and eight patients, with various dermatoses, were treated by corticosteroid injections, and followed up for at least six months and in most instances for a longer period. The effects of hydrocortisone acetate, 25 mg./c.c., and of 6-methylprednisolone (Depo-Medrol), 25 mg./c.c. and 40 mg./c.c., were compared. Uniformly, treatment by 6-methylprednisolone in the stronger concentration was more effective than in the weaker dilution, and the weaker dilution was more effective than equal amounts and concentrations of hydrocortisone. The practical indications in a number of disorders are discussed. No systemic effects occurred and no permanent local atrophies were observed.

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SPECIAL ARTICLE

SOME APPLICATIONS OF STATISTICS TO MEDICAL RESEARCH

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PART II OF FOUR PARTS

THE "*t*" TEST

THE "*t*" test is used to determine whether or not the observed difference between two comparable means is significant. It involves the assumption of a null hypothesis, namely, that there is no real difference between the means. The conclusion of the test is that the null hypothesis is either accepted and there probably is no real difference, or rejected, in which case there probably is a real difference between the means. Suppose we wish to compare the serum cholesterol levels of healthy adults within a specific age group living on two islands, A and B. The method of collecting the samples and the chemical determination of the amount of cholesterol should be the same in each case. The chemical method should be a reliable one which will give reproducible results with a minimum of error. Error due to technique will occur at random and will be added to the natural variability of the population.

On island A we select at random from the population 100 people according to the details of the experiment. We calculate the mean serum cholesterol level and the standard deviation. These values are referred to as statistics as they are only estimates of the true population values which are called parameters. The parameter is most often unknown or incalculable. Suppose that the mean cholesterol level is 248 mg. % and the standard deviation 8 mg. %. On the basis of these 100 determinations we can say that 68% of the population who meet the requirements of the experiment will have cholesterol levels between 240 and 256 mg. % (248 ± 1 S.D.), 95% will be between 232 and 264 mg. % (248 ± 2 S.D.) and 99% will be between 224 and 272 mg. % (248 ± 3 S.D.).

The standard deviation refers to further single values; for example, if another person were selected from the population there would be a 68% chance that his serum cholesterol level would be within the range, mean ±1 S.D. If the patient has a value beyond the 3 S.D. limits he has only a 1% chance of having a normal cholesterol level. Therefore the difference between his cholesterol level and that of the normal population must be explained on the basis of some factor other than chance, e.g. a disease process.

If another 100 people were selected from the population and the serum cholesterol determined by the same method and under the same experimental conditions, we would get another range of values and another mean and standard deviation. Probably the new mean would be close to the first, and to the true population mean. For each new mean that is calculated there will be a standard error, and this may be called the standard error of the mean, and is calculated as follows: standard error of the mean,

$$s_{\bar{x}} = \frac{\text{S.D.}}{\sqrt{n}}.$$

"*n*" is the number of variates in the sample. In the above example the mean was 248 mg. % and the standard deviation 8 mg. %. The standard error of the mean therefore is

$$\frac{8}{\sqrt{100}} = 0.8 \text{ mg. \%}.$$

This means that if further samples were selected from the population and the mean calculated, in 68% of the new samples the mean would lie between 248 ± 0.8 mg. % (mean ±1 standard error of mean), in 95% between 248 ± 1.6 mg. % (mean ±2 standard error of mean) and in 99% between 248 ± 2.4 mg. % (mean ± 3 standard error of mean). The new means will be approximately normally distributed about the true population mean regardless of the kind of distribution of the population from which the sample was drawn. If the means are normally distributed and since the standard deviation for the population is constant, then the ratio $\bar{x}$/S.D. will also be normally distributed. Student* showed that this could be used as a test of significance and worked out a frequency distribution for $\bar{x}$/S.D. which he designated as *Z*. Later he determined the distribution of $\bar{x}/s_{\bar{x}}$ which, with modification by Fisher, is the modern "*t*" test. The formula which he used is $t = (\bar{x}_d/s_{\bar{d}})$.

We repeat the experiment and calculate the mean and standard deviation for 100 people on island B. For purposes of simplification five people for each island will be considered.

The basic formula that is used is

$$t = \frac{\bar{x}_d}{s_{\bar{d}}} = \frac{\text{difference between two means}}{\text{standard error of the difference between two means}}$$

The standard error of the difference between two means is calculated as shown in the first equation at the top of page 488.

If we look in a table of "*t*" (such as is found on page 443 of "Methods of Statistical Analysis"[3]) we find across the top probability values of 0.5, 0.10, 0.05, 0.02, 0.01 and 0.001, and down the left-hand side D.F. This refers to the degrees of freedom which may be defined as the number of categories that may be arbitrarily filled. From a group of five people, only

*Pseudonym of W. S. Gosset.

$$s_{\bar{d}} = \sqrt{\frac{\text{S.D.}_1^{\,2}}{n_1} + \frac{\text{S.D.}_2^{\,2}}{n_2}}$$

$$\text{where S.D.}_1 = \sqrt{\frac{\Sigma(X_1)^2 - [(\Sigma X_1)^2/n_1]}{n_1 - 1}}$$

$$\text{and S.D.}_2 = \sqrt{\frac{\Sigma(X_2)^2 - [(\Sigma X_2)^2/n_2]}{n_2 - 1}}$$

Serum Cholesterol Mg.%

Island A		*Island B*	
X_1	$(X_1)^2$	X_2	$(X_2)^2$
240	57,600	230	52,900
250	62,500	225	50,625
240	57,600	235	55,225
255	65,025	235	55,225
255	65,025	240	57,600
Σ=1240	Σ=307,750	Σ=1165	Σ=271,575
$\bar{x}_1$= 248		$\bar{x}_2$= 233	

$$\text{S.D.}_1 = \sqrt{\frac{307{,}750 - (1240^2/5)}{5 - 1}}$$

$$= \sqrt{\frac{307{,}750 - 307{,}520}{4}}$$

$$= \sqrt{\frac{230}{4}} = \sqrt{57.5}$$

$$= 7.6$$

$$\text{S.D.}_2 = \sqrt{\frac{271{,}575 - (1165^2/5)}{5 - 1}}$$

$$= \sqrt{\frac{271{,}575 - 271{,}445}{4}}$$

$$= \sqrt{\frac{130}{4}} = \sqrt{32.5}$$

$$= 5.7$$

$$\bar{x}_d = \bar{x}_1 - \bar{x}_2 = 248 - 233 = 15$$

$$s_{\bar{d}} = \sqrt{\frac{57.5}{5} + \frac{32.5}{5}} = \sqrt{11.5 + 6.5}$$

$$= \sqrt{18} = 4.24$$

$$t = \frac{15}{4.24} = 3.5$$

four can be chosen at random; for the fifth there is no choice. In the example there are four degrees of freedom for each group of results, giving a total of 8 D.F., i.e. $n_1 + n_2 - 2$. Looking in the table of "*t*" go down the D.F. column to 8 and across the top to 0.05, 0.01 and 0.001. These are the values of "*t*" at 5%, 1% and 0.1% probability and they are 2.31, 3.36 and 5.04 respectively. For 8 D.F. and a "*t*" value of 2.31, if there is no real difference between the two means, the observed differences would be expected to occur due to chance alone in 5% of cases. Similarly with "*t*" values of 3.36 and 5.04 the observed differences would be expected to occur due to chance in only 1% and 0.1% of cases respectively. In the above example the "*t*" value was 3.5. This means that the observed differences would be expected to occur in less than 1% of cases if chance were the only factor. Thus there is less than 1 chance in 100 that the observed difference is due to chance. The difference between the two means is very likely a real one.

If the "*t*" value had been less than 2.31, we would conclude that the observed difference would occur due to chance in over 5% of cases and that there probably was no real difference between the two sets of figures.

If the experiment has been designed such that the data may be logically paired, for example readings taken on the same subject before and after a procedure, then the calculation of "*t*" is different from that shown in the preceding example. However, if pairing is logical but there is an unequal number of values in each category, the calculation of "*t*" must be done according to the previous illustration (unpaired data).

An example of an experiment designed to permit pairing of data is as follows. According to a predetermined experimental design, measurements were taken of the systolic blood pressure of eight people before and after administration of a certain drug, with the following results:

Systolic Blood Pressure

	Before (X_1)	*After* (X_2)	$X_1 - X_2$	$(X_1 - X_2)^2$
Subject 1	130	120	+10	100
Subject 2	135	155	−20	400
Subject 3	125	140	−15	225
Subject 4	135	155	−20	400
Subject 5	140	140	0	0
Subject 6	120	115	+5	25
Subject 7	115	145	−30	900
Subject 8	100	130	−30	900
Σ	1000	1100	−100	2950

$$\bar{x}_1 = \frac{1000}{8} = 125,\ \bar{x}_2 = \frac{1100}{8} = 137.5,\ \bar{x}_2 - \bar{x}_1 = 12.5$$

$$t = \frac{\bar{x}_d}{s_{\bar{d}}} = \frac{\text{difference between two means}}{\text{standard error of the difference between two mea}}$$

The standard error of the mean is

$$s_{\bar{x}} = \frac{\text{S.D.}}{\sqrt{n}} = \sqrt{\frac{\Sigma X^2 - [(\Sigma X)^2/n]}{n(n - 1)}}$$

and the standard error of a difference between two means is

$$s_{\bar{d}} = \sqrt{\frac{\Sigma(X_1 - X_2)^2 - [(\Sigma X_1 - \Sigma X_2)^2/n]}{n(n - 1)}}$$

Substitution in the equation of the values from the above table gives the following:

$$s_{\bar{d}} = \sqrt{\frac{2950 - [(1000 - 1100)^2/8]}{8(8 - 1)}}$$

$$= \sqrt{\frac{2950 - (10000/8)}{56}}$$

$$= \sqrt{30.36}$$

$$= 5.51$$

Substituting in the equation

$$t = \frac{\bar{x}_d}{s_{\bar{d}}} = \frac{12.5}{5.51} = 2.27$$

The number of degrees of freedom is one less than the number of pairs, i.e. $8 - 1 = 7$.

In the table of "t" for 7 degrees of freedom, the "t" values for probabilities of 0.05 and 0.01 are 2.36 and 3.50. The calculated value of "t" is 2.27. The probability of obtaining this "t" value is slightly more than 5%. Therefore, the observed difference in systolic blood pressure before and after administration of the drug would be expected to occur due to chance alone in slightly more than 5% of all eight-subject series. Since this is very close to the arbitrarily set level of significance of 5%, it is obvious that the results are probably inconclusive and the experiment should be repeated using a larger group of subjects.

Fiducial Limits

Fiducial or confidence limits are limits of an interval on either side of the calculated mean between which there is a known probability that the true population mean lies. To calculate the fiducial limits the following formula is used:

$$t = \frac{\bar{x} - m}{s_{\bar{x}}}.$$

"m" is the population mean difference and in the above examples was equal to 0. If we transpose the above and using $\pm t$, we get

$$\pm t s_{\bar{x}} = \bar{x} - m \qquad m = \bar{x} \pm t s_{\bar{x}}$$

Letting "t" take its value at $p = 0.05$ and 0.01 and the appropriate degrees of freedom, we will have the limits between which there is a 95% or 99% chance that the true population mean lies.

For example, island A:

$m = \bar{x} \pm t s_{\bar{x}}$ $\quad$ t at 5% for 4 D.F. is 2.78

$$\bar{x} = 248 \qquad s_{\bar{x}} = \frac{\text{S.D.}}{\sqrt{n}} = \frac{7.6}{\sqrt{5}} = \frac{7.6}{2.2} = 3.5$$

$$\therefore \quad m = 248 \pm (2.78 \times 3.5) = 248 \pm 10.7$$

The interpretation of this is that there is a 95% probability that the true population mean lies between 248 ± 10.7 mg. %. These are the confidence or fiducial limits. The upper limit is 248 + 10.7 and the lower limit 248 − 10.7 mg. %.

Summary

The "t" test is a method of determining whether two means are significantly different from one another. The theory of the test and its application are described with the use of examples.

CASE REPORT

GUNSHOT WOUND OF THE PREGNANT UTERUS WITH SURVIVAL OF THE FETUS

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Thirty-three cases of gunshot wounds of the pregnant uterus, collected from a review of the previous literature or encountered in personal experience, were reported by Kobak and Hurwitz in 1954.[1] This report concerns an additional case which presented certain unusual aspects.

Kobak and Hurwitz's cases dated back to 1845. There were three maternal deaths, all of which occurred before 1912. Fetal mortality was 55% among those patients who were judged to have a viable fetus at the time of injury. There were 15 vaginal deliveries among the 33 cases reported, in all of which labour commenced within a few hours up to 17 days after the accident. The fetal mortality among those who had vaginal deliveries was 66%; among those who had abdominal deliveries, it was 46%. In one case the spent bullet was lodged extradurally in the baby's head and was removed surgically.

The patient was a 25-year-old woman, para IV, gravida XII, whose last menstrual period had occurred December 7, 1959. She was first seen on May 26, 1960. At that time she gave a history of having shot herself in the abdomen one month previously, when she was approximately 25 yeeks' pregnant. On the day of the accident, she had been admitted to another hospital where she stayed for about 10 days without treatment. She returned home feeling well, except for the complaints described below.

When she was seen on May 26, she complained of weakness in the right leg, intermittent vaginal bleeding

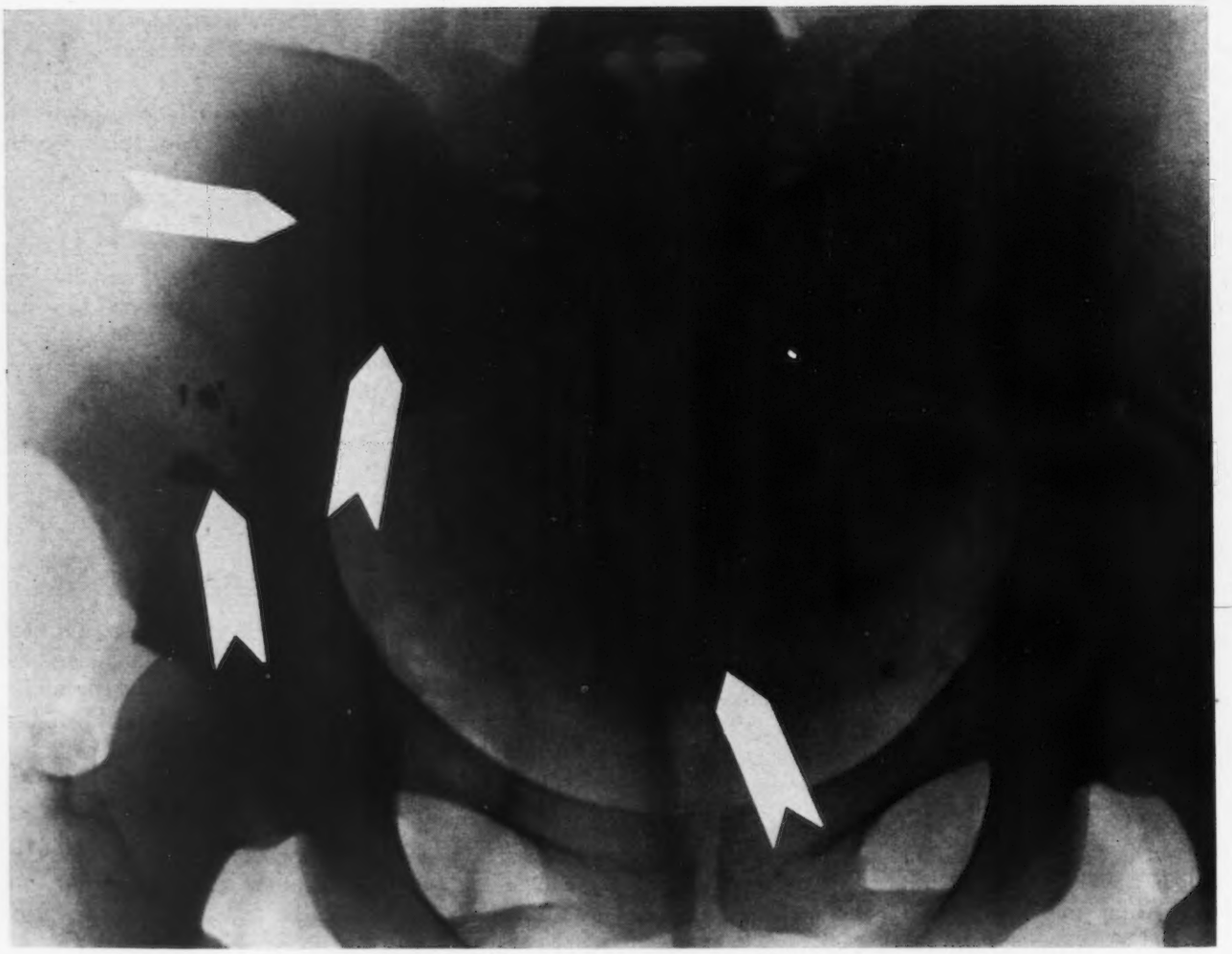

Fig. 1.—Showing a small fetus lying transversely across the pelvis and metallic fragments adjacent to the right iliac bone.

and a weight loss of 25 lb., all of which dated from her accident.

Physical examination was essentially negative except for the following findings: The uterine fundus was palpable at the level of the umbilicus. There were obvious fetal movements but the fetal heart was not heard. There was a small round red scar about 0.4 cm. in diameter, 3 cm. below and to the left of the umbilicus. Pelvic examination revealed no bleeding, but there was a yellow-brown vaginal discharge. The cervix was closed.

The circumference of the right thigh was about two inches less than that of the left thigh. The patient was unable to elevate the right leg while lying supine, and there was marked weakness of the vastus medialis and intermedius. The right knee and ankle reflexes were less active than those on the left. Plantar responses were normal.

Roentgenogram of the abdomen (Fig. 1) revealed fragments of the bullet adjacent to the right iliac bone and a small fetus lying across the pelvis, its head to the right and legs to the left.

It was felt that the bullet was lying near the femoral nerve and had damaged part of it. It was considered that if the nerve did not regenerate spontaneously, the bullet would have to be removed surgically and the nerve sutured if necessary, after the fetus had been delivered.

The patient continued to have intermittent vaginal bleeding, at times quite severe, but refused to cooperate or accept her physician's advice. During this time she thought that her leg symptoms were improving.

On July 29, 1960, she was admitted, in labour, to the Gatineau Memorial Hospital and was found to have a breech presentation. She was delivered without difficulty of a 5 lb. 13½ oz. male baby.

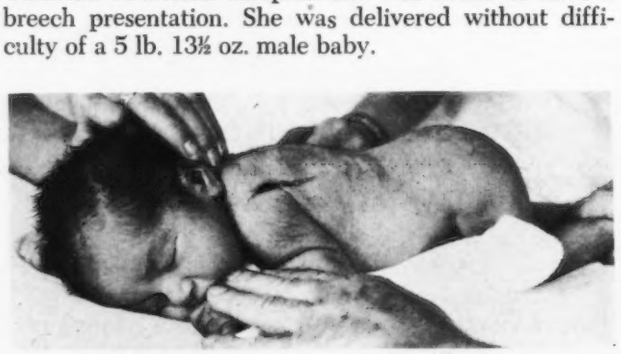

Fig. 2.—Photograph of newborn infant showing superficial wound over the left scapula.

The baby was found to have a superficial wound over his left scapula. This wound was 8 cm. long and ran vertically from near the acromion process down to the lower angle of the scapula. The extremities of the wound were healed, but its central portion was open for a distance of about 2.5 cm. and was filled with healthy granulation tissue (Fig. 2). There was no evidence of skeletal injury, so radiographic studies were not carried out on the infant. The baby became slightly jaundiced and developed a mild degree of diarrhea with melena. The following day he had some

hematemesis. On the third postpartum day he was transfused with 100 c.c. of blood. He gradually began to improve and was discharged well on August 15, 1960.

COMMENT

Kobak and Hurwitz recommended that all such patients should be subjected to immediate laparotomy as in the case of any patient with a gunshot wound of the abdomen. The subsequent treatment depends upon several factors. If the fetus is dead or previable and the uterine damage is not extensive, the uterus may be sutured and a vaginal delivery allowed. The uterus is capable of a satisfactory, normal labour if the wound is small and well repaired, without danger of rupturing. Extensive uterine damage would be an indication for Cesarean section or possibly hysterectomy. When the maternal condition is good, the state of the fetus is a factor of importance in the choice of treatment. If the mother's condition is poor, however, as little surgical trauma as possible is indicated. Bowel and uterine perforations should be repaired and the abdomen closed. In the extreme state when the patient is moribund and the fetus appears to be viable, a Cesarean section is probably indicated.

SUMMARY

At approximately the 25th week of gestation, a 25-year-old woman sustained a through-and-through bullet wound of the pregnant uterus, injuring the fetus and resulting in partial loss of function of the patient's femoral nerve. The pregnancy continued for a further 10 weeks and terminated in a breech delivery of a normal baby. The superficial wound over the baby's scapula was not completely healed in 10 weeks of intrauterine life.

REFERENCE

1. KOBAK, A. J. AND HURWITZ, C. H.: *Obst. & Gynec.*, 4: 383, 1954.

SHORT COMMUNICATION

INFLUENCE OF ENVIRONMENTAL TEMPERATURE ON SURVIVAL OF PREMATURE ANIMALS*

ALBERT B. BROWN, M.D. and
C. ALAN B. CLEMETSON, B.M.,
Saskatoon, Sask.

WHILE IT is customary to keep premature babies in warm incubators, there have been suggestions in recent years that those with respiratory difficulty might have an improved chance of survival if they were cooled. Cross *et al.*[2] have produced evidence that even mild hypoxia in the newborn human infant decreases its metabolic activity and therefore leads to a fall of body temperature. The question arises whether one should combat this fall in temperature by artificial warming or take advantage of the hypothermia in the hope of diminishing the oxygen requirements of the newborn infant in proportion to the diminished oxygen supply.

Westin *et al.*[3] have succeeded in perfusing previable human fetuses with oxygenated blood at room temperature and were able to keep their hearts beating for three or four hours; they found that the period of survival was diminished if the temperature of the fetus was maintained at 37° C. and concluded that the higher metabolism of the warmed fetus exhausted more quickly its limited supplies of oxygen, glucose and other nutritive elements. However, cooling of viable infants may lead to shivering and result in an increased tissue oxygen consumption, which would be undesirable in the presence of respiratory distress. Thus, the prevention of shivering becomes important and would have to be achieved by the administration of ataractic drugs.

Furthermore, Bower *et al.*[1] have described a group of 70 hypothermic babies admitted to the Birmingham Children's hospital with a diagnosis of "primary cold injury". Delay in wrapping the baby after birth, tight wrapping and failure to heat the room at night were thought to be the main causes of chilling. One-quarter of these babies died and pulmonary hemorrhage was a constant finding at necropsy.

Thus, there are arguments for and against the maintenance of body temperature in newborn infants with respiratory difficulty, and one is left in considerable doubt as to the proper treatment. The present study of piglets delivered prematurely by Cesarean section was designed in an attempt to elucidate this and certain related problems.

METHOD

The pulmonary syndrome of the newborn occurs mainly in premature infants, especially those delivered by Cesarean section. Therefore, it was decided to perform Cesarean sections on suitable animals before term and to study the factors influencing the survival of their young. Several species of animals were considered for this study,

*From the Department of Obstetrics and Gynecology, University of Saskatchewan.

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Fig. 1.—Showing a small fetus lying transversely across the pelvis and metallic fragments adjacent to the right iliac bone.

and a weight loss of 25 lb., all of which dated from her accident.

Physical examination was essentially negative except for the following findings: The uterine fundus was palpable at the level of the umbilicus. There were obvious fetal movements but the fetal heart was not heard. There was a small round red scar about 0.4 cm. in diameter, 3 cm. below and to the left of the umbilicus. Pelvic examination revealed no bleeding, but there was a yellow-brown vaginal discharge. The cervix was closed.

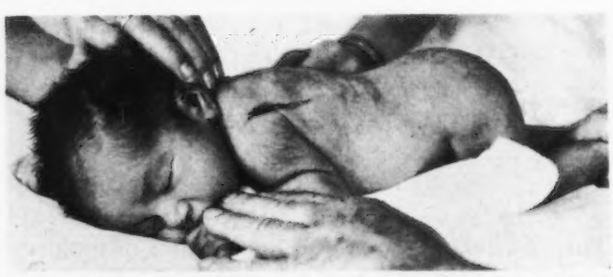
The circumference of the right thigh was about two inches less than that of the left thigh. The patient was unable to elevate the right leg while lying supine, and there was marked weakness of the vastus medialis and intermedius. The right knee and ankle reflexes were less active than those on the left. Plantar responses were normal.

Roentgenogram of the abdomen (Fig. 1) revealed fragments of the bullet adjacent to the right iliac bone and a small fetus lying across the pelvis, its head to the right and legs to the left.

It was felt that the bullet was lying near the femoral nerve and had damaged part of it. It was considered that if the nerve did not regenerate spontaneously, the bullet would have to be removed surgically and the nerve sutured if necessary, after the fetus had been delivered.

The patient continued to have intermittent vaginal bleeding, at times quite severe, but refused to cooperate or accept her physician's advice. During this time she thought that her leg symptoms were improving.

On July 29, 1960, she was admitted, in labour, to the Gatineau Memorial Hospital and was found to have a breech presentation. She was delivered without difficulty of a 5 lb. 13½ oz. male baby.



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METHOD

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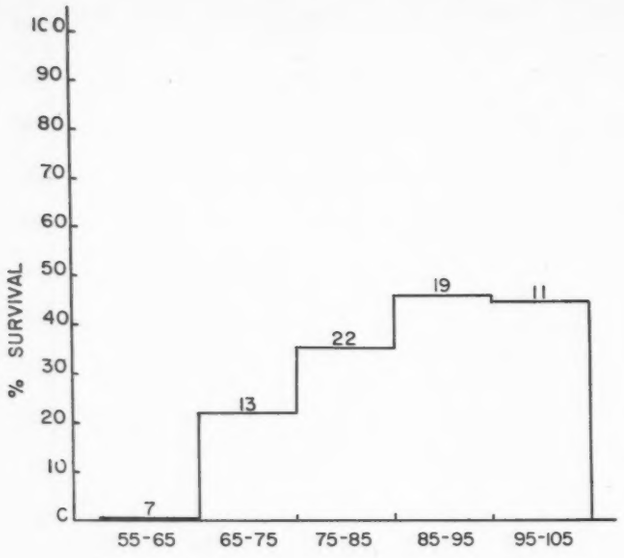

Fig. 1.—Environmental temperature in °F.

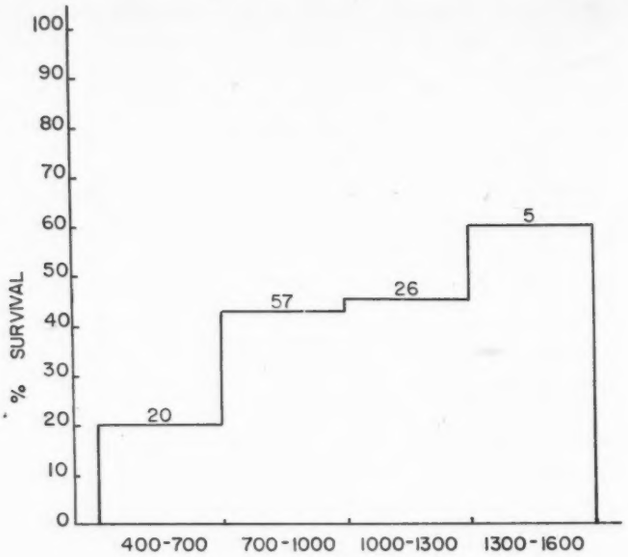

Fig. 2.—Birth weight in grams.

and some initial work was performed on dogs and sheep. It was eventually decided that pigs were more suitable for our purposes.

A pure breed of Yorkshire pigs is maintained by the Animal Husbandry Department of the University of Saskatchewan, and it was through the co-operation of this department that we were able to obtain bred sows of known maturity. Normally, these sows farrow 16 weeks after mating, but we have been delivering the piglets by Cesarean section 7 to 12 days before their expected date of farrowing. Cesarean sections have now been performed on 17 sows, and 126 premature piglets have been obtained for study. General anesthesia for pregnant sows weighing between 350 and 400 lb. has provided quite a problem for the Department of Anesthesia, but various techniques have been investigated and many of the problems have been solved. Anesthesia was usually induced with 1 or 2 g. of sodium hexobarbital or sodium thiopental injected into an ear vein, after which the sow was lifted on to the operation table and tied on her back. Anesthesia was maintained by various techniques, including open drop chloroform, ether and local infiltration, but it is our impression that hexobarbital induction followed by endotracheal ether was the most satisfactory method.

After delivery from the sow, whose body temperature was between 101 and 102° F., the piglets were distributed among three incubators, one warm (95 to 105° F.), one at medium temperature (75 to 95° F.) and one cold (55 to 75° F.).

The warm and medium incubators were fitted with heating appliances, and the cold incubator with a cooling unit. The temperature of each incubator was controlled by a thermostat and this was changed for each experiment so that a range of temperatures from 55 to 105° F. could be studied. All the piglets were breathing air throughout these experiments, and the two air vents of each incubator were left open to ensure this. No drugs were administered to the piglets, which were distributed among the three incubators in the order of their delivery as: 1—hot; 2—medium; 3—cold; 4—hot; 5—medium; 6—cold, etc. They were kept under close observation in these incubators for two days. Hourly temperature, pulse and respiration records were kept, together with observations of their behaviour. All piglets dying within the two days of observation were subjected to postmortem examination.

RESULTS

Since we were unable to obtain sow's colostrum for these piglets and since it is known that piglets stand a very poor chance of survival unless they obtain colostrum, the survival figures for the group as a whole were poor.

Seventy-six piglets delivered from 11 sows were included in the hot, medium and cold incubator experiments, but only 72 of these piglets were alive at the time of introduction to the incubators.

Fig. 1 shows the percentage survival of all 72 piglets in 10° F. groups. It is evident from this graph that their optimum environmental temperature lies between 85 and 95° F., in which range there was a 47% two-day survival. However, the results for the 95 to 105° F. range are little different, with a survival of 45%. No piglets survived for two days at environmental temperatures below 70° F.

If we consider the length of time that the piglets survived, 74° F. seems to be a very definite cut-off point, for only three of 13 lived longer than 15 hours at temperatures below 74° F., while 58 out of 59 lived longer than 15 hours at temperatures above 74° F. This difference in survival time is significant at the 1% level.

Shivering was noted in piglets in all three incubators, but it did not prevent a steady fall in the body temperature of those in the cold incubator.

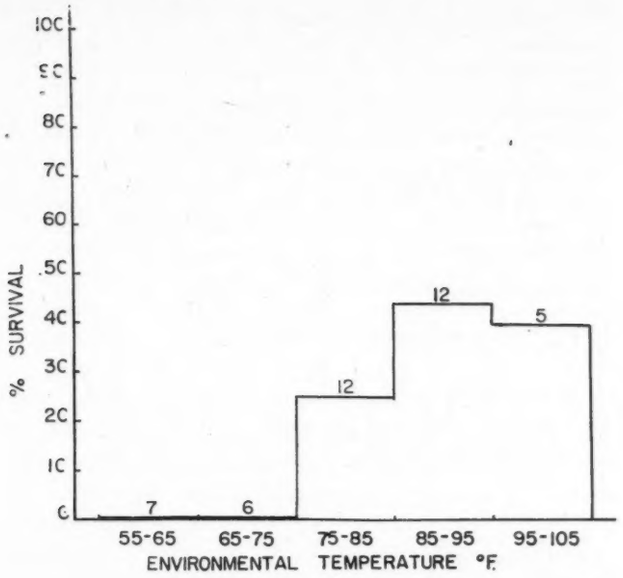

Fig. 3.—Piglets less than 1000 g.

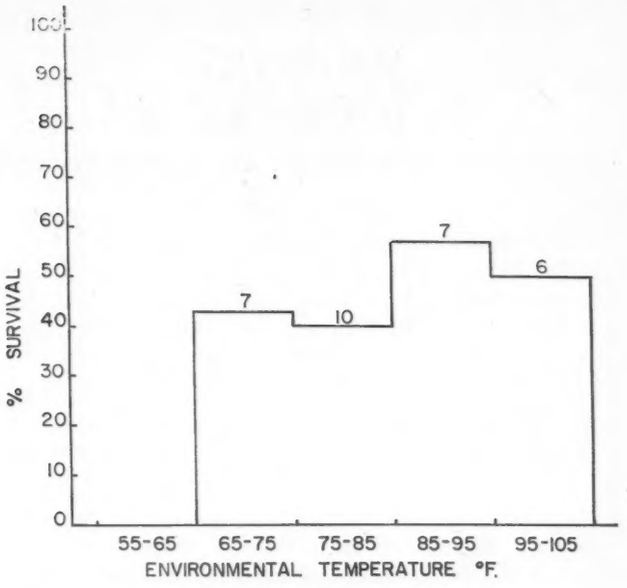

Fig. 4.—Piglets more than 1000 g.

Fig. 2 shows the relationship between birth weight and survival in these premature piglets.

Figs. 3 and 4 show the same data as Fig. 1, but Fig. 3 includes only the 42 piglets weighing less than 1000 g., and Fig. 4 shows only those 30 piglets weighing more than 1000 g. Here again, the optimum environmental temperature for survival seems to be 85 to 95° F. in both weight groups, but it is evident that the smaller piglets as a group do not stand as good a chance of survival as the larger ones. Indeed none of the piglets weighing less than 1000 g. survived for two days at environmental temperatures below 75° F.

Intrapulmonary hemorrhage and atelectasis were the principal causes of death in these piglets, but diarrhea and fluid loss from scours may have been a contributory cause of death in some instances.

SUMMARY AND CONCLUSIONS

Premature piglets definitely show an improved survival rate if they are kept warm. There was no evidence in the experiments carried out to suggest that cooling *per se* was beneficial, even to those showing respiratory distress. It is theoretically possible that hypothermia produced by cooling associated with the use of histotoxic drugs might be beneficial, but we have no evidence on this point.

This study was assisted by funds provided by the Child and Maternal Health Grant No. 607-13-12 of the National Health Grants Program.

We wish to thank Dr. W. Howell of the Department of Animal Husbandry for his co-operation and Mr. C. L. Kaller of the Department of Mathematics for his statistical analysis of the data. We are also greatly indebted to Drs. G. M. Wyant, J. H. Harland and A. M. Keil of the Department of Anesthesia.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

FOOD STANDARDS

From some points of view, it seems rather surprising that the proposal to enact legal definition and standards of quality for foods and drugs should create any anxiety, or awaken anything more than academic interest. Among a people perfectly informed, and perfectly honest, the proposal could have no more meaning than the construction of a dictionary of technical terms; it would not affect business in any way. In such a state it could only be through accident that substitution of one article for another might occur. Government surveillance would not be needed; and expert supervision would only be required by the manufacturer as a guide in production. Of course all this is Utopian, and can only be realized in a future when we shall need neither military nor police forces.

The recognition of human frailty, and the temptation offered by our adoption of the prevailing business principle, buy in the cheapest market and sell in the dearest, compels the buyer to seek protection by legal means. For, while it is true that ignorance on the part of those who supply the market may, at times, unwittingly endanger the health and the pocket of the consumer, it is abundantly evident that, in the main, it is not ignorance which supplies the sophisticated food and drug products that flood our markets today. On the contrary, a very high degree of technical and special knowledge is possessed by, or is at the service of, the producer. The discoveries and advances of physics and chemistry are capable of being employed alike in the interest of honesty and of dishonesty. Science itself is neither moral nor immoral; it is simply unmoral. — A. McGill, *Canadian Medical Association Journal*, 1: 232, March 1911.

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BLINDNESS IN CANADA

IT IS estimated that over 78 million persons throughout the world today are afflicted by the grim tragedy of blindness. In Canada, where the number of blind persons in 1960 totalled 23,800, the administration of an integrated national program directed towards the prevention, control and cure of this disability and the welfare of those it now affects, is centred in a single authority, the Canadian National Institute for the Blind.

Registration as a blind person and eligibility for blindness allowance in Canada are based on the Canadian Ophthalmological Society's definition of blindness which is incorporated in the Blind Persons Act: "When the visual acuity of the better eye, after correction with the proper refractive lens, is 6/60 (Snellen) or less:—or with better than 6/60 in one or both eyes but with limitation of both fields of vision such that the widest diameter of the visual field subtends an angle of less than 20 degrees."

Comparison of blindness prevalence in Canada with that of other nations is difficult and probably not meaningful because of the wide variations in criteria for its definition, and in methods of collecting statistical data on the numbers of persons affected. Of all the nations of the world, Canada alone possesses a system of national registration that extends throughout the ten provinces and includes the Indians and Eskimos of the Yukon and Northwest Territories. In 1960 the incidence of blindness as here defined was 132 per 100,000 Canadians.

Two intensive surveys of the causes of blindness have been reported from this country, the first by Aylesworth in 1945 and the most recent by MacDonald in 1954. The latter study, based on analysis of data on 18,998 of the 20,506 persons then registered with the C.N.I.B., provided the following breakdown:

TOPOGRAPHICAL CLASSIFICATION

Cataract	4861 cases
Hereditary lesions	2944 "
Glaucoma	2017 "
Retinopathy	1718 "
Myopia	1420 "

ETIOLOGICAL CLASSIFICATION

Poisoning	226 cases
Infection	1162 "
Congenital disease	3648 "
Systemic disease	1847 "
Attributable to war	103 "
Trauma	1067 "
Undetermined and unknown cause	11,019 "

The distribution of blindness by age groups and its shifting emphasis towards the later years of life are revealed by further analysis of C.N.I.B. records:

	1945
1 to 20 years of age	2414 cases
21 to 40 " "	2139 "
41 to 60 " "	4469 "
60 years and over	3630 "

	1954	*1960*
Under 7 years of age	277 cases	282 cases
7 to 20 years of age	1027 "	1603 "
21 to 39 " "	2841 "	3083 "
40 to 64 " "	6910 "	7501 "
65 to 69 " "	2331 "	2369 "
70 to 99 " "	7104 "	8937 "
100 years and over	16 "	25 "

Thus, while 28.7% of blind persons in 1945 were over 60 years of age, the proportion of those over 65 rose to 47.6% in 1960, and it is of interest that in the latter year 25 were 100 years of age or older.

These statistical data exclude the much larger number of individuals in whom blindness is confined to one eye, who probably outnumber officially registered blind persons by about four to one.

Blindness does not usually develop suddenly. Frequently its evolution includes a prolonged twilight period of considerable economic significance because it is at this stage that occupational capacity decreases slowly but inexorably.

There are several critical periods in life when eye care is particularly important and when such care may alleviate or occasionally prevent future blindness. (1) As soon as the child can count fingers, or even before this if corneal opacities or squints are evident. Early and adequate care of strabismus is of *urgent* concern, since the prognosis for adequate vision is poor if a squint has been present for as long as half of the child's life. Prompt treatment not only prevents visual loss in the squinting eye but improves subsequent binocular vision, as well as the cosmetic result. (2) At school age. (3) In the late teens if visual work causes discomfort. (4) In the early forties. (5) In the early fifties, when bifocal lenses are commonly required. (6) After the age of 60 years, re-assessment of ocular status should be carried out periodically.

Certain trends in the patterns of blindness and in the eye diseases that may result in blindness have

become apparent and are worthy of note. In a high proportion of cases of blindness the underlying nature of the causative factor or factors remains unknown. In this group of disorders, which includes cataracts, glaucoma, retinal detachment, familial, hereditary and some congenital lesions, more intensive investigative study and research is particularly required. Operations are now being performed for cataracts as soon as visual work becomes difficult, without waiting for the cataract to "ripen" or mature as has been the custom in the past. While it used to be said that the victim of glaucoma would die blind if he lived long enough, more effective drugs and methods of care make this statement no longer true. The development of new and better antibiotics has reduced considerably the amount of blindness resulting from infections and injuries. Ophthalmia neonatorum, once the cause of 28% of blindness in childhood, is now only occasionally encountered. Trachoma, responsible for one-quarter of the world's blindness, is rare in Canada though it does occur among our 150,000 Indian and 11,000 Eskimo citizens. The recent discovery of the viral agent responsible for trachoma holds forth promise that an effective vaccine may become available for prevention and/or treatment of this disease. Retrolental fibroplasia, recognized in 1942 as a catastrophic cause of blindness in premature infants, was eventually linked with the administration of high concentrations of oxygen in the neonatal period. Early and effective action to combat this cause of blindness in Canada was taken in 1953 by the Central Committee in Ophthalmology for the Royal College of Physicians and Surgeons of Canada and the Canadian Ophthalmological Society. Nutritional deficiencies are not prominent as a cause of blindness in Canada but were considered responsible in the cases of 54 veterans registered with the C.N.I.B., who suffered prolonged periods of nutritional deprivation in Japanese prison camps during the Second World War. Better protective and educational measures and the provision of early and adequate care in industry are gradually reducing the occupational causes of blindness. Visual loss due to ocular complications of congenital and acquired syphilis is becoming progressively less frequent.

The total economic loss to Canadians due to ocular discomfort, twilight vision and actual blindness, together with pensions and costs of personal care for the blind, probably exceeds one hundred million dollars. A greater degree of financial support is required by ophthalmic centres throughout Canada to permit expansion and acceleration of their research in all aspects of blindness prevention. A Canadian institute of ophthalmology and a well-equipped library of ophthalmic literature are additional objectives to be striven for in furthering the campaign against blindness in this country.

A.E.M.

THE BACTERIOLOGIST SHOULD RETURN TO THE WARDS

THROUGH the fault of no one in particular, the bacteriologist has of recent years, in his modest and retiring way, become ensconced in his laboratory, there to commune in solitude with his numerous specimens. As a result he has tended to become more and more purely a technician, not using his total medical knowledge. This is a situation which is entirely unsatisfactory not only for bacteriologists and clinicians but for patients as well.

The bacteriologist should return to the wards where his advice is badly needed. Antibiotics are no longer the universal panacea they were once thought to be. Many have been used too readily and without due consideration of consequences. To counter this undesirable state of affairs it is essential that the knowledge of the bacteriologist in regard to antibiotic resistance to drugs be released from its seclusion in the laboratory and brought to the bedside of the patient, in consultation with the other physicians and surgeons concerned with the details of patient-care.

Such direct participation of the bacteriologist in the deliberations of the treatment team is being provided in other parts of the world, as Ericsson, of the Department of Bacteriology in the Karolinska Sjukhuset, Stockholm, points out in a recent monograph.[1] The bacteriological services in the Karolinska Institute have been organized to function as an integrated department of the hospital, where they have contributed materially to the practice of medicine in its laboratory and clinical aspects.

At the Karolinska Hospital a number of basic principles have been established for the use of antibiotics. The first obvious need is that the bacterial etiology of the disease being treated, and the sensitivity to antibiotics of the organism involved, be established. The decision to use the antibiotic of choice is reached after due and careful consideration of the general condition of the patient and the probable prognosis of his disease. When an antibiotic is used, dosage levels should be high in order that the drug may exert its maximum effect. Subtherapeutic doses of antibiotics should be uniformly avoided, except when they are to be used as a prophylactic measure in special situations, as in the case of patients with previous rheumatic fever, osteomyelitis or bacterial endocarditis. In most situations low dosages favour the development of resistant strains of organisms, quite clearly an unsatisfactory situation.

With a return of the bacteriologist to the wards, his critical approach could greatly assist in the more effective use of antibiotics.

W.H.LER.

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CUTANEOUS SENSITIVITY TO NEOMYCIN

THE number of patients with contact dermatitis due to neomycin encountered in dermatological practice has been increasing sharply, parallel with a rising number of case reports of neomycin sensitivity in the medical literature.[1-8]

There are several unusual features relative to the development and manifestations of sensitivity to this antibiotic that may obscure its recognition and diagnosis. Cutaneous sensitivity to neomycin develops in an insidious manner; the lesions under treatment do not respond to what normally would be considered adequate therapy or they progress slowly despite such therapy. Only about one-quarter of patients sensitive to this drug show positive routine patch tests while their intradermal tests are regularly positive. Many of the shotgun-types of preparations being advocated by various pharmaceutical manufacturers for topical use in the treatment of skin disorders contain combinations of neomycin with corticosteroids such as hydrocortisone. When these preparations are used the manifestations of sensitivity to neomycin are likely to be masked by the anti-inflammatory effect of the steroid, which may account for the insidious and obscure nature of such sensitivity reactions in some cases. Strong cross-sensitization to other antibiotics may exist, as evidenced by the 101 patients with positive sensitivity reactions to both neomycin and bacitracin, reported by Pirila and Rouhunkoski[9] and the cross-reactions to neomycin and streptomycin described by Sidi *et al.*[5] Such cutaneous sensitivity is more common in cases of otitis externa.[8] Neomycin is generally considered to be a rare cause of cutaneous sensitivity and consequently most physicians view it with a low index of suspicion in this regard. This is an additional factor that tends to obscure the recognition of neomycin contact dermatitis.

Over the past few years large quantities of neomycin have been applied to the skin of vast numbers of patients in the treatment of a wide variety of cutaneous disorders. While the incidence of dermal sensitivity to this antibiotic is probably low, it appears to be increasing, and it is difficult to predict the course that this trend may assume in the future. There is no doubt that patients with eczematous skin lesions tend to develop cutaneous sensitivity more readily than do those who are not subject to eczema; consequently it would seem prudent to use other antibacterial agents such as iodochlorhydroxyquin in the topical therapy of infected eczema. Antibiotics may be used with care and for short periods of time in the local treatment of simple skin infections such as impetigo. R.J.

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RENAISSANCE OF A FAMOUS HOSPITAL

LAST year the Hospital of the Charité of Berlin celebrated its 250th anniversary. Over the years the staff of this world-renowned institution has included some of the most illustrious names in the history of medicine. Johannes Müller, Schönlein, Virchow and Koch from an earlier day, and later such scientists as Ehrlich, Abderhalden and Warburg, pathologists of the stature of Rössle, Ascheim and Zondek and leaders of humanistic and social progress like Grotjahn and Nicolai, have graced its medical faculty and made outstanding contributions to its fame. During the Hitler regime the forces of national socialism inflicted heavy losses upon this venerable institution and forced 120 members of its medical staff to give up their teaching activities. Racial persecution, antisemitism and fascist pogroms reduced the quality of German medicine and isolated it from international science in many fields.

Since 1945, one hundred million marks have been spent to repair and rebuild the clinics and institutes of the Charité and restore it once again to its position of eminence among German hospitals. The Charité, located in the Soviet zone of Berlin, is now a teaching hospital of Humboldt University, which numbers on its medical faculty some 60 professors and teachers, 500 physicians and research workers and 4000 other employees. The hospital itself has 2633 beds and an annual admission rate of 27,000 inpatients and 390,000 outpatients. Eight hundred students are currently being enrolled yearly in the medical faculty of Humboldt University, which now has a total enrolment of nearly 3000 medical undergraduates and has once more become a leading force in the scientific medical world of Germany.

In association with the activities commemorating the hospital's 250 years of service the faculty organized a memorial celebration of the fiftieth anniversary of the death of Robert Koch, a scientific conference on medical education, and symposia on philosophy and medicine and on modern methods of teaching medical sciences. Reports of significant scientific investigations by many of the faculty members will be published to commemorate the occasion, and the university's lecturers are being stimulated to work towards higher academic qualification.

The faculty has expressed its intent to resist all forces of discrimination and, in a proclamation (*Deutsche Gesundheitswesen*, 15: 1991, 1960), has gone on record as sharply condemning the manifestations of antisemitism being reported with increasing frequency in western Germany.

Despite the unmistakable overtones of political propaganda in the proclamation, the medical world will welcome the evidence of rehabilitation of this famous medical landmark. W.G.

LETTERS TO THE EDITOR

INTRA-ARTICULAR CORTICOSTEROID THERAPY

To the Editor:

I thank Dr. Woodbury (*Canad. M. A. J.*, 83: 1271, 1960) and Dr. Keith Palmer (*Ibid.*, 84: 120, 1961) for their gentle replies to my warning against the use of intra-articular steroid injections (*Ibid.*, 83: 1271 1960). Perhaps my warning should have said that I am also a lawyer limiting my law work to legal medicine and consider it my duty to warn medical colleagues of possible traps.

The *British Medical Journal* reference by Dr. Keith Palmer is not the only warning in the literature about atrophy following steroid injections. The article and bibliography by Golding and Begg should also be consulted (*Brit. M. J.*, 2: 1129, 1960). Unpleasant reactions that my colleagues and I at Elizabeth Hospital had from intra-articular injections made us give them up three years ago and caused me to inquire in Britain. Colleagues in neighbouring areas of Arkansas, Oklahoma, Missouri and Kansas also see reactions which are alarmingly painful and temporarily disabling. Right now I am endeavouring to prevent a woman with a painful reaction from suing the doctor who injected her shoulder in a neighbouring town. It is possible that techniques here, in neighbouring states and in London were faulty, but I believe it more reasonable that some people react unduly.

Is there any valid reason for injecting joints with steroids? Before injections were done and after we abandoned them, good results were obtained using steroids by mouth. "First of all, do no harm." Why use a complex method when a simple one suffices?

The thousands of injections quoted by Drs. Woodbury and Palmer would be impressive were it not for the memory of thousands of injections given years ago to cure duodenal ulcer. Many ulcers perforated; some of the patients died. Phylacogen injections, spleen extracts and vaccines were given literally by the million. Dinitrophenol for obesity slew its share of victims. All of these products were lauded then as much as intra-articular steroids are now.

A famous European teacher said, "Experience! What is experience? You make the same mistake 10,000 times and call it experience!" As doctors we should "enter the temple of science through the portals of doubt."

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[For a report on further experiences with the use of intra-articular corticosteroid therapy, see *Medical News in Brief*, page 498.—ED.]

MEDICAL RECORDS AND HOSPITAL ACCREDITATION

To the Editor:

With reference to the letter from Dr. John R. Sandford of Deep River, Ont. (*Canad. M. A. J.*, 83: 1167, 1960), might I be permitted to make the following comments?

With respect to the recommendations which follow a survey of a hospital by a member of the Canadian Council on Hospital Accreditation, surely this is the purpose of such a survey. Can anyone deny that, without unprejudiced, intelligent observations from qualified people who are entirely unbiased towards any hospital, there would be a general tendency to "let down" in the over-all efficiency of operation and of the standard of patient care? Left to our own devices, it is an unfortunate truth that we are inclined to become complacent and self-satisfied in our daily efforts, whatever our chosen profession.

The requirements of the C.C.H.A. with regard to the examination of tissues removed are not in any way intended to be a reflection on the integrity and capabilities of a surgeon. In many ways such examinations act as a safeguard, not only to the patient, but to the surgeon and the hospital as well. And while examination of prepuces or hernial sacs may seem of a trivial nature, an agreement between the medical staff and the pathologist requiring only a gross examination and report does not seem to be unreasonable.

Reporting on other tissues, besides providing the protection mentioned above, can also lead to thinking and discussion among members of the medical staff, and anything that leads to thinking in these days of automation is to be welcomed.

It is not the intention of the C.C.H.A. to differentiate between a hospital of 25 beds and one of 1200 beds when it comes to the standard of care given a patient. In these days of ever-changing medical therapy, what might have been inevitable 25 years ago is now unforgivable.

Certainly a hospital of 25 beds or even 120 beds without interns is not expected to maintain medical records to the extent of a teaching hospital, but it is expected that the fundamentals as outlined for accreditation will be included in the medical record so that intelligent follow-up care may be given the patient by any physician.

FREDERICK T. TAYLOR,
Medical Records Librarian

Grande Prairie Municipal Hospital,
Grande Prairie, Alberta.

Canad. M. A. J.
Mar. 4, 1961, vol. 84

MEDICAL NEWS IN BRIEF

INTRASYNOVIAL CORTICOSTEROID THERAPY: A DECADE OF USE

At the Arthritis Clinic of the University of Pennsylvania Hospital, hydrocortisone acetate was first injected into arthritic joints in January 1951. Since then, more than 100,000 injections of corticosteroids have been given into the inflamed joints, bursae or tendon sheaths of about 40,000 patients. In a report of their experience over this 10-year period (*Bull. Rheumat. Dis.*, 11: 239, 1961), Hollander, Jessar and Brown conclude that intrasynovial steroid therapy has proved its usefulness as a temporary, palliative, repeatable, local adjunct in the treatment of a variety of rheumatic manifestations.

Instability developing in a repeatedly injected weight-bearing joint was noted in 37 joints of 26 cases, almost equally divided between rheumatoid and osteoarthritic patients, a total incidence of 0.7%. While it is unknown whether or not this instability, from relaxation of ligaments and partial absorption of bony margins, was due to steroid injections, it could be regarded as a complication of therapy. Such joints had been in continued weight-bearing use and often had been traumatized by falls due to muscle weakness and ligamentous relaxation. There was no loss of sensation or proprioception in such unstable joints: they did not resemble a Charcot joint. In only four joints, two rheumatoid arthritic hips, one osteoarthritic hip and one osteoarthritic knee, was the absorption of bone extensive. In the hips "aseptic necrosis" of the femoral head was found at operation, and a prosthesis was inserted in the joint. The knee was fused when a similar softening of the tibial condyles was found.

Intra-articular corticosteroid therapy, therefore, does not stop the progression of rheumatoid arthritis or the degeneration of osteoarthritis, but the risk of unusual or accelerated deterioration of the joint is less than 1%. The physician and patient must ask themselves whether it is better to risk an ankylosed, contracted or painfully useless joint rather than the slight possibility of an unstable, relatively painless joint which is still functional with orthopedic support. This suggests the need for periodic x-ray examination of any joint subjected to repeated steroid injection. Also, weight-bearing arthritic joints should be protected against undue trauma or excessive use while under intra-articular steroid therapy.

RECENT ADVANCES IN TREATMENT OF THE CANCER PATIENT

More advances have been made in the past 15 years in the various fields of cancer than in many preceding decades. Many of the more dramatic discoveries have been in areas of basic research and their true significance is yet to be elucidated. Improvements in surgical results have been related largely to increases in the amount of tissue excised with the tumour, improved knowledge of surgical physiology (better preoperative and postoperative care) and better anesthesia. Cole remarks that further improvement of results by increasing the extent of operation is not to be expected, because the limit of operation is already extended to vital structures (*J. A. M. A.*, 174: 1287, 1960).

Improving the patient's nutritional status preoperatively results in an appreciable decrease in morbidity and mortality. Soap and water preparation of the skin over a palpable tumour may produce enough manipulation to dislodge tumour cells and should be avoided. Preoperatively and at operation, all tumours must be handled gently to minimize cancer cell dissemination. Irrigation of the wound with cancericidal agents is effective in animals and merits trial studies in humans. Blood vessels supplying the tumour area should be ligated early in the operation to prevent vascular dissemination of dislocated cells. Perfusion and adjuvant therapy with anticancer drugs deserve clinical trials, but better anticancer agents must be developed before satisfactory results can be expected from these procedures. Recent experimental evidence suggests that patients with advanced cancer do not possess significant immune factors to destroy inoculated cancer cells but that young normal individuals without cancer possess some type of immune factor which will destroy cancer cells after inoculation. The first evidence that humans produce anticancer antibodies was published in 1955 by Graham and Graham (*Cancer*, 8: 409, 1955) who used the complement-fixation test for this purpose. These observations emphasized the need for further explorations of immunological mechanisms involved in patients with neoplastic disease and suggest possible implications for the future development of immunotherapeutic measures.

MORPHOLOGIC INVESTIGATIONS OF THE ORIGIN OF AORTIC ATHEROSCLEROSIS

According to Thoma, a pathologist of the early twentieth century, arteriosclerosis is a compensatory endarteriopathy, developing as a result of localized or diffuse weakness of the media. It leads to a widening of the lumen, slowing of blood flow, secondary thickening of the intima, fat deposition and atheromatous ulceration. All other changes are compensatory.

Felix Marchand contested this theory, at least in its general form, pointing out that the thickening of the intima can be found without any damage to the media. Other authors have found that certain experiments could lead to widening of the carotid arteries without any thickening of the intima.

Doerr (*Deutsche med. Wchnschr.*, 85: 1401, 1960) investigated a group of cases in which there was a suspicion that aortic atherosclerosis arose from an inflammatory or allergic basis, and attempted to relate the medial disease, "rheumatic aortic sclerosis", to the localization of the most pronounced areas of atherosclerosis. According to Klinge, rheumatic sclerosis is usually localized in the lumbar aorta. In the years following World War II, coincident with improved nutrition, a marked increase of ulcerative aortic sclerosis of the lumbar region was observed in Western Germany. Since 1955 Doerr has carried on an investigation in an attempt to answer the following questions: (a) Does arteriosclerosis begin in the intima or in the media? (b) What are the conditions which lead to development of medial malacia and has this real significance in the pathogenesis of arteriosclerosis? (c) Does rheumatic

aortic sclerosis exist and how can it be recognized histologically? The details of this investigation are described and the histologic preparations of intima and media illustrated.

On the basis of these investigations the author arrives at the following conclusions: Rheumatic arteriosclerosis is rare, although it exists. It resembles histologically that of syphilitic mesaortitis, and the process develops along the vasa nutritia of the media. In infectious diseases the author observed localized necrosis of the media followed by "aortite en plaque". These lesions are completely different from the disease known as arteriosclerosis. Here, changes in the intima consisting of paralysis of the musculature, with degeneration or necrosis on the one hand, and destruction of elastic fibres on the other, lead to a flattening of the aortic wall with levelling of the intima and loosening of the media. Once edema has developed, the process progresses to lipid deposition from the plasma. In most cases the sclerosis increases towards the periphery and is maximal in the lumbar aorta, although cases are recognized in which sclerosis is maximal in the lower thoracic aorta. The areas where maximal mechanical stress exists are those most liable to develop arteriosclerosis.

Arteriosclerosis develops through plasmatic infiltration of the intima. This, however, leads to advanced changes only in the presence of: (a) a "humoral factor" (appropriate plasma conditions); (b) a vascular permeability factor; and (c) structural and other changes in the vessel wall which are as yet not completely understood. When contact points between smooth muscle and elastic layer have been loosened and diffusion spaces appear, permitting the deposition of edema fluid, mucopolysaccharides, lipoproteins and other metabolites, only then can the clinical and anatomical picture of arteriosclerosis of the aorta develop.

(Continued on advertising page 36)

Medical News from Parliament

Of recent interest and importance to the medical profession was the announcement by the Honourable Davie Fulton, the Minister of Justice, of a new policy in regard to drug addiction, its prevention and treatment.

The program has two main aspects: steps that will be taken by the Federal Government in the field of purely federal authority, and measures that may be taken in co-operation with the Provinces if they so wish, in areas where the authority is primarily provincial.

Under the first head, important changes will be made with respect to the apprehension, trial and sentencing of offenders, as well as with respect to their treatment while within our institutions, and their supervision after release. The full program envisages the establishment by the Federal Government, as soon as possible, of special institutions for the segregation and treatment of drug addicts. The timing of the establishment of new institutions, and their nature, will depend to a considerable extent on the degree to which the Provinces wish to co-operate.

In order to enable the system to produce the most effective results with respect to criminal addicts, legislative changes will be made to provide procedures for the determination of the question of whether an accused is an addict, and to provide further that if so found, and if convicted of the charge of illegal possession, appropriate sentence to "custody for treatment" may be imposed. The legislation will also provide for release from custody only upon approval by the national parole board and under supervision for an indeterminate period and upon terms to be laid down by that agency. Those so sentenced will of course be committed to the new institutions as soon as they can be set up. The new institutions will be operated under the present federal penitentiary system, but will include the most up-to-date program for treatment of addicts.

The program will also provide for increased penalties for those involved in trafficking drugs. Under this approach, the law and the enforcement of it will be based on the view that the trafficker who peddles drugs primarily to pay the cost of his own addiction is no less a menace to society, while at large, than the trafficker who peddles for some other purpose. Details of legislation will be announced in due course, but it is generally proposed to provide that anyone convicted of trafficking may be sentenced to imprisonment for life, and in the case of a second or subsequent offence, will automatically receive an indeterminate sentence.

The Minister of National Health and Welfare has established a committee to study and report upon improved methods for dealing with the non-criminal addicts, and this committee will be working in co-operation with the provincial departments of health. It is anticipated that a few centres will be established in suitable locations where a trained staff can study methods of treatment and guidance of non-criminal addicts. These would be community-based services with emphasis on follow-up and prevention of reversion to addiction.

In addition, in order to be able to deal with recalcitrant individuals who are not amenable to treatment in a community centre, we have proposed to the Provinces that they provide a procedure, under provincial legislation, for the referral of suspected addicts for medical and psychiatric examination and for committal for treatment of those found to be addicts. Such persons could then be committed for treatment to the new federal institutions.

It is hoped that with co-operation between various levels of government with an attack that stresses prevention and treatment, this very distasteful and degrading affliction will be better controlled.

H. M. HORNER, M.D., M.P.

Canad. M. A. J.
Mar. 4, 1961, vol. 84

THE LONDON LETTER

HAILSHAM'S LAW

For over ten years the British Medical Association has been campaigning for the right of private patients in the United Kingdom (and there appear to be quite a number of these) to have their drugs free, on the grounds that Mr. Bevan originally promised that the new National Health Service "or any part of it" should be available to everyone. Since the private patient has to pay his contribution to the government anyway, it may be argued that he should be entitled to get at least his drugs for his money. Many members of Parliament appear to have been won round to the B.M.A.'s way of thinking, but a new twist to the perennial argument was given the other day in the House of Lords when a Conservative lord, Lord Hailsham, made a pronouncement which will no doubt go down in history as "Hailsham's Law".

It has been pointed out that a Conservative manifesto issued in 1949, called *The Right Road for Britain*, issued when the party was out of office, contained the following promise: "We shall allow private patients to obtain free of charge drugs prescribed by their doctor on a parity with people in the State scheme". It is only fair to say that a little later, at the time when the Conservatives started their winning series, this promise did not appear in the next manifesto. Lord Hailsham's dictum is that: "When you lose an election you are not bound by the promises in your election manifesto." This dictum needs some interpretation. Does this mean that a party which lost an election can then regard its defeat as giving it absolution for all time from any promises made at that time? And if this is so, ought it not to tell the electors at the next contest that it has changed its mind? This is the sort of thing which electors should watch out for, and it might further be noted that the noble lord's dictum has come in for some nasty remarks from members of his own party, one of whom said publicly that it "was nothing less than disgraceful".

MEDICINE ON RADIO AND TV

As in North America, the subject of health and disease is a much exploited one on radio and television. Since a British governmental committee on broadcasting was appointed under the able chairmanship of Sir Harry Pilkington to consider the future of British radio and TV, it was natural for the British Medical Association to prepare evidence for it on the rather vexed subject of medicine in these mass media. The B.M.A. memorandum of evidence indicates that this body has come a long way in its thinking in the last few years. It gives a general approval to the use of the media for health education, and feels that the sympathetic presentation of programs which deal with the work of doctors helps to give the public a better understanding of the profession's contribution to the community. It emphasizes that co-operation between doctors and broadcasters is essential, and hopes that eventually a panel of medically qualified advisers, and possibly a full-time medical editor for the services, may be established.

Some ground has been yielded on the question of anonymity of medical broadcasters or telecasters. The final decision is now left to the individual doctor, and the only bar to mention of his name should be when such mention is likely to result in his "obtaining patients or promoting his own professional advantage". The memorandum states that any correspondence addressed to radio or TV doctors should not be forwarded to them. It adds that the standard of medical programs in Britain is high, but emphasizes the need for more attention to programs on prevention to the exclusion of more dramatic ones. Both documentary and fictional programs are approved. The radio doctor must not attempt to replace the family doctor, or enter into detailed discussion of symptoms, prognosis or therapy. The B.M.A. suggests a monthly magazine program of items from various medical fields, and the use of regional programs in such instances as the occurrence of local epidemics.

The memorandum then takes a slap at medical advertising on privately owned TV (there is none on the BBC programs). Ideally, the B.M.A. feels that any advertisement encouraging self-medication should be prohibited. If not, then a medical committee should pass on all material submitted and turn it down if it appeared to make unjustifiable claims. One critic of this suggestion has pointed out in a newspaper that this last suggestion is a two-edged sword. The public is already only too prone to believe all it sees on TV, and if it thought that the advertising was endorsed by doctors the last state as regards self-medication might be worse than the first.

DRUG ADDICTION

Drug addiction in Britain is a minor problem in comparison with its prevalence in some parts of North America. Nevertheless there is a black market in drugs here, and it is encouraging to read an article by Lady Frankau and Dr. Stanwell (*Lancet*, December 24, 1960) on the results of their treatment of 51 drug addicts between August 1958 and March 1960. These were all on cocaine, heroin, morphine or pethidine, and there were three groups: (1) Nine who had been given the drug for adequate medical reasons and then become dependent. All are now cured. (2) Six middle-aged patients of high intellectual attainments who had taken the drug to "live more fully" originally and used it for up to 20 years. Three are now clear of dependence, and two on the way to attaining this state. (3) Thirty-six younger patients of unstable and immature characters, aged 18-32, completely selfish and irresponsible, and living only for their drug. Even in this unpromising group 20 have been cleared of dependence.

Withdrawal was accomplished in an institution, after psychotherapy to give insight and ensure co-operation. Tranquillizers were freely used, and one of the troublesome factors in later treatment was to get the patient away from the pedlars. However, with the decline in trade, two of the pedlars themselves became patients and the black market in this group seems to have died away.

S. S. B. GILDER

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Mar. 4, 1961, vol. 84

THE MEDICO-LAY AFFILIATES OF THE CANADIAN MEDICAL ASSOCIATION

THE CANADIAN NURSES' ASSOCIATION

[This is the second of a series of articles describing the organization and work of the voluntary health agencies and other medico-lay bodies affiliated with the Canadian Medical Association.]

THE CANADIAN NURSES' ASSOCIATION is a federation of the ten provincial registered nurses' associations; it is the national association for over 60,000 graduate registered nurses in Canada. Founded in 1908 as the Canadian National Association of Trained Nurses, it became known as the Canadian Nurses' Association in 1924, and in 1947 was incorporated by a special Act of Parliament. Membership is by virtue of membership in a provincial association and includes membership in the 46-member International Council of Nurses. The C.N.A. is the third largest association in the International Council of Nurses and is affiliated with the World Health Organization and the World Council of Health. The C.N.A. conducts a program for the exchange of nurses between Canada and other countries; it also sponsors study tours in Canada for nurses of other countries and for Canadian nurses abroad.

The Canadian Nurse, a journal edited and published by the Canadian Nurses' Association, is the official organ of the association and now has a circulation of well over 60,000. The journal provides a flow of information on general and technical developments in Canadian nursing.

The Executive Committee is elected by the membership and is composed as follows: Voting members — president, three vice-presidents, the immediate past president, the ten provincial association presidents; four members from the nursing sisterhoods, chairman of the Journal Board of *The Canadian Nurse* and the chairmen of the five key national committees, namely: Nursing Service, Nursing Education, Public Relations, Legislation and By-Laws, and Finance. The non-voting members are the executive secretaries of the ten provincial nursing associations; the executive director of the journal, *The Canadian Nurse*; and the general secretary-treasurer of the Canadian Nurses' Association. The executive committee meets annually; national committees hold regular meetings to conduct the business of the Association and to guide its program. The objects of the Association are: to dignify the profession of nursing by maintaining and improving the ethical and professional standards of nursing education and service; to encourage its members to participate in affairs promoting the public welfare; to promote the best interests of the nurses of Canada and to maintain national unity among them; and to encourage an attitude of mutual understanding with the nurses of other countries.

The C.N.A. holds a general meeting every two years in the form of a biennial convention. The 1960 meeting was held in Halifax; in 1962 the Association will meet in Vancouver. Every member of the Association may present her views at this national forum.

To attain its objectives the C.N.A. employs a paid executive staff of professional nurses and appropriate clerical staff, and maintains a national office in Ottawa. The policies and program of the Association are established by the membership through representation on the Executive Committee. National Committee members act as spokesmen for individual nurses on matters within the scope of their activities. Findings and recommendations of the C.N.A. may be accepted or rejected by each provincial association.

The C.N.A. Committee on Legislation and By-Laws and the national office staff are continually aware of, and recommend action if necessary on, legal developments that may affect the registered nurse in Canada. The C.N.A. makes its views known on behalf of all nurses on legislation for national health insurance. The Association's public relations program is designed to promote understanding and fuller acceptance of nursing aims, including the development of a better understanding of the position and duties of the professional nurse in relation to other health and nursing personnel.

The C.N.A. works closely with many other national bodies. It is a member of the Board of Governors of the Victorian Order of Nurses for Canada; the Canadian Association for Adult Education; the Canadian Commission on UNESCO; the Canadian Council on Nutrition; the Canadian Joint Committee on Nursing; the Canadian Welfare Council; the Defence Medical Dental Services Advisory Board; the Health League of Canada; and the National Council of Hospital Auxiliaries. The Association is represented on Nursing Advisory Committees of the Canadian Red Cross Society; St. John Ambulance Society; Victorian Order of Nurses for Canada, and Civil Defence, Department of National Health and Welfare.

The Association is an associate member of the Canadian Hospital Association and the Canadian Medical Association.

ACHIEVEMENTS OF THE C.N.A.

In 1927 a study of nursing education in Canada was undertaken in co-operation with the Canadian Medical Association, and the resultant report by Dr. G. M. Weir gave a comprehensive factual statement of nursing conditions in Canada, with a statement of recommendations at the close of each chapter. The findings of the Weir report are still basic to many of the nursing activities and studies being carried on today.

The C.N.A., with financial assistance from the Canadian Red Cross Society, conducted an experiment in nursing education at the Metropolitan Demonstration School of Nursing in Windsor, Ontario, from 1948 to 1952. The report of this experiment by Dr. A. R. Lord gives valuable data concerning the length of time necessary for the preparation of a professional nurse.

In 1953, at the request of the C.N.A., the Research Division of the Department of National Health and Welfare carried out a Study of the Functions and Activities of Head Nurses in a General Hospital. This study has been widely used throughout Canada in the allocation of nurses' duties and in salary adjustments.

The C.N.A. has presented official statements to the Federal Government, Royal Commissions, and various organizations representing nursing in Canada. The two most recent were briefs on financial assistance for nursing education.

The Association has initiated Policies of Nursing Education and Nursing Service for use throughout Canada. Institutes and conferences, which affect the future progress of nursing education and nursing service, are held at regular intervals. A pension plan for its members was inaugurated in 1958.

Publications are prepared with a view to improving nursing service generally, and the status of nursing. Recent publications include "Spotlight on Nursing Education", "A Manual for Head Nurses in Hospitals" and "Toward Improved Job Satisfaction".

In spite of many problems, the Canadian Nurses' Association can look back on many years of steady progress. The C.N.A. has endeavoured to be equal to the tasks and responsibilities with which it has been confronted. It has gained valuable experience and has laid the foundation for greater efforts in the future.

The most recent achievement of the Association was the completion of the Pilot Project for Evaluation of Schools of Nursing in Canada. The major concern for the next few years will be the implementation of the recommendations of this report.

The Association will initiate a study of the whole field of nursing education in Canada and, at the same time, conduct a school improvement program. A study of the nursing services where the students receive their clinical experience is another major project to be undertaken by the Association.

Further information about the Association may be obtained from: The General Secretary, Canadian Nurses' Association, 74 Stanley Avenue, Ottawa, Ontario.

MEDICAL MEETINGS

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

SCIENTIFIC SESSIONS, 1961 MEETING*

SYMPOSIUM ON "SOME INTERESTING ASPECTS OF ENVIRONMENTAL MEDICINE"

The members of the panel were introduced by the Chairman, *Dr. K. J. R. Wightman,* Professor of Medicine of the University of Toronto.

Dr. Morley G. Whillans, Assistant Chief Scientist of the Defence Research Board, Ottawa, opened the symposium with a general discussion of medical problems of life under special environmental conditions and their significance, dealing briefly with three main types of response to environmental challenges: (a) evolutionary or genetic, (b) immediate and long-term physiological and biochemical responses of adaptation and acclimatization, and (c) psychological and sociological responses and the process of learning how to manage and to tolerate environmental conditions. In summing up his discussion of these factors, Dr. Whillans observed that man is achieving greater control of his climatic environment even though its mastery is not yet foreseeable. Supraphysiological means that have been evolved now enable him to work and to live practically anywhere. The environmental problems that man creates for himself may prove more complex and subtle. The increasingly sedentary character of his life with relatively low demands on physical efficiency but with increasing demands on mental ability, and the complexities created by man himself, represent a major environmental challenge. An aggressive, imaginative scientific response to this challenge will affect, perhaps profoundly, the degree of success achieved in surmounting environmental problems and probably the future development of man as a species.

Medical problems of life under conditions of arctic cold were discussed by *Dr. J. A. Hildes,* Director of the Arctic Medical Research Unit of the University of Manitoba. By any definition, he said, the arctic provides a wide range of conditions, not only geographic and climatic, but even more important are the social conditions of arctic life, ranging from those of technicians in radar sites to those of certain Eskimo communities where life still depends only in small part on imported materials. Dr. Hildes presented evidence refuting the usual portrayal of the Eskimo living in his native habitat as a vigorous and fit hunter free of those degenerative diseases that beset more civilized cultures. The native Eskimo does indeed suffer from such degenerative disorders, including the widespread manifestations of atherosclerosis and a broad range of malignant neoplasms as well. The incidence of these diseases and their relation to diet, genetic background and arctic living are not yet established and it is possible that important information concerning their etiology might be forthcoming from more intensive demographic studies of such population groups. Regarding the finding that many common and some uncommon infectious diseases have been found to occur in both endemic and epidemic forms in this region, the relation to arctic cold is probably not a direct one and these endemics and epidemics are more likely concerned with the cultural habits of the arctic inhabitants so afflicted. The prevalence of such infections in this area is, however, of potential importance to intruders from without, and the study of small isolated communities may throw added light on the natural history of certain of these infections whose significance is still obscure. The occurrence of certain less common infections and infestations such as trichinosis, psittacosis and hydatid disease in the arctic has now been recognized and there are other interesting medical or physiological problems, such as the hypermetabolic state of Eskimos, that await further study. Dr. Hildes empha-

*For Parts 1 and 2 of this report of the Scientific Sessions, see pages 397 to 402, issue of February 18, and pages 443 to 447, issue of February 25.

sized again, in closing, that in most cases the relation of the special medical problems of arctic life to arctic cold appears to be at best an indirect one.

Professor F. C. MacIntosh, head of the Department of Physiology at McGill University, in his discussion of the medical problems of underwater depths, observed that man in an underwater environment must take an air bubble with him. The main problems of underwater medicine, therefore, are those of keeping this air fit to breathe. Man has devised various means of overcoming this problem, ranging from the air hose, the umbilical cord of the professional deep sea diver, to the various types of self-contained underwater breathing apparatus (SCUBA). Despite the impressions created by science fiction, the mechanical crushing effect of pressure in the depths is not a significant problem. Pressure only creates problems by the fact that the pressure of gas supplied to the lungs must be adjusted to physiological limits.

The limits to which man can descend to underwater depths, like the limits of other barriers of nature, are established only to be broken through. The present record for underwater diving, set by a Royal Navy diver, is 600 feet. The major medical hazards in deep sea diving are: (1) Decompression sickness. (2) Inert gas narcosis, picturesquely dubbed "the raptures of the depths". Here, as in the case of decompression sickness, nitrogen again is the culprit. The narcotic properties of inspired air increase with depth, till, at about 150 feet, they are approximately equivalent to the effects of six ounces of rye on an empty stomach. Waxing theological, Dr. MacIntosh commented that we are all possibly slightly drunk all the time, from the nitrogen in the air we inspire, and he wondered if this were not the logical explanation for original sin. (3) Oxygen toxicity: At high pressure, pure oxygen is a deadly poison which causes permanent oxidation of enzymes of the cerebral cortex through combination with their sulfhydryl groups and may result in a cortical discharge with manifestations similar to a major epileptic seizure. Dr. MacIntosh suggested the intriguing hypothesis that many years of breathing oxygen might possibly produce certain harmful changes in man, for example the changes we attribute to ageing. If these problems presented by the toxicity of oxygen at high tension could be eliminated, the depths to which divers could descend would be extended considerably, possibly to as much as 2000 feet. (4) Mechanical difficulties in breathing associated with even the best apparatus yet devised; these as a rule are minor medical problems.

Even shallow water diving presents certain physiological and medical hazards, which include: (1) "Shallow water blackout" due to inadequate carbon dioxide regulation. This probably results in most cases from faulty carbon dioxide removal by the soda lime in the diver's air cannister with the result that the diver anesthetizes himself with his own CO_2. (2) Anoxia. (3) "Trapped gas" problems, including "burst lung" and air embolism, ruptured eardrums, sinus barotrauma and expansion of gas in the alimentary canal. Regarding the latter, Dr. MacIntosh advised against the consumption of champagne immediately before a diving venture.

He noted that civilian diving, both professional and amateur, is gaining rapidly in popularity. This entails certain hazards with which physicians should be familiar. Much of the breathing gear leaves a great deal to be desired. Divers themselves are not sufficiently familiar with the risks involved. The effective treatment of severe decompression sickness demands immediate recompression in a specially designed chamber, under medical supervision. Only one such recompression chamber is currently available in Canada. Dr. MacIntosh recommended that portable chambers be provided, at strategic centres scattered across the country, capable of being transported rapidly by helicopter to any area where they might be required. On the whole, he felt that shallow water diving is a healthful, pleasure-giving sport which should not be too vigorously over-regulated, but considered that it would probably be desirable that all amateur divers should belong to clubs, with periodic educational instruction by qualified physicians.

Wing Commander R. A. Stubbs, of the R.C.A.F. Institute of Aviation Medicine in Toronto, soared into the ionosphere in a fascinating discourse on environmental considerations involved in the manning of high-altitude aircraft and space satellites. The altitude to which air-breathing craft can ascend is limited by the fact that they require enough air to provide sufficient aerodynamic lift, and maintain altitude, and by the fact that aircraft structures fail at certain limits of heat to which they are subjected in high-altitude flight, though these limits may be extended somewhat by the development of new ceramics and other materials with great heat-resisting properties. If the velocity of an aircraft can be adjusted so that it can be propelled just far enough and fast enough that its propulsive force is counterbalanced by the gravitational force of the earth, it will go into orbit in what has been termed the "corridor of continuing flight". Beyond this corridor lies the zone of space flight. Physiological problems involved in space flight include those presented by (1) the decrease in atmospheric pressure with increasing altitude, (2) the changes in atmospheric temperatures through various zones in ascent, and (3) the decrease in partial pressure of oxygen with increasing altitude. Above 10,000 feet it is necessary to add oxygen to the atmosphere if flight is to be maintained without physiological mishap. The amount of added oxygen needed increases with further ascent until, between 30,000 and 38,000 feet, 100% oxygen is required for respiration. Above this altitude it is necessary to provide oxygen at greater than ambient pressure (pressure breathing), which is tolerable up to altitudes of about 48,000 feet. Beyond this the increased pressure required in the inspired atmosphere creates so many physiological problems that it is necessary to provide counter pressure from within the body by such devices as the anti-G suit. Up to altitudes of 55,000 to 60,000 feet this can be accomplished by a partial pressure suit but at still higher altitudes a full pressure suit covering the entire body surface area is necessary. Since the complex problems of providing such suits for all space-flight personnel and maintaining them in a continuous state of foolproof serviceability are so great, the answer seems to lie in the provision of a pressurized cabin with a common atmosphere for all its occupants. In subsequent discussion, Dr. William Franks drew a picturesque parallel between such a pressurized cabin and a "flying anesthetic machine treating a number of patients simultaneously".

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Additional medical problems associated with space flight are presented by the presence of minor gas constituents in the atmosphere, the regulation of partial pressure of carbon dioxide, the generation of ozone and its toxicity, and the generation of peculiar complex molecules from new synthetics used in space-craft construction. Another major medical hazard of space travel beyond what Dr. Franks termed "the earth's greenhouse that we live in" is posed by intense ionizing radiation in the outer atmosphere. Protective equipment necessary to combat this radiation with materials now available would weigh several tons.

SYMPOSIUM ON "THE IRRADIATION HAZARD IN CANADA"

This panel was under the chairmanship of *Dr. O. H. Warwick*, Senior Physician, the Ontario Cancer Institute, Toronto.

Dr. D. Harold Copp, Professor of Physiology, University of British Columbia, provided the introductory background for the panel with an outline of the frontiers of radiation which have posed increasingly complex problems to man since November 8, 1895, when Professor Roentgen first observed the peculiar penetrating radiations that emanated from an electrically excited Crookes tube. The ill effects of overexposure to x-rays did not take long in making their appearance. As these continued to take their toll, an X-Ray and Radium Protection Committee was set up in Great Britain in 1921. In 1929 the International Commission on Radiological Protection (ICRP) was established and it still exercises a most important function in setting standards and recommending upper limits for permissible exposure. Soon after Roentgen's discovery, additional sources of ionizing radiation were added in increasing number, from the highly radioactive element, radium, the effects of which eventually caused the death of its discoverer Madame Curie, to the modern developments of nuclear physics, and the more ominous products of applied atomic physics.

The radiations whose potentially dangerous effects are of particular concern are of several types, all of high energy and productive of ionization; and all of which cause injury to tissue. Professor Copp proceeded to explain and define such forms of ionizing radiation as alpha and beta particles, gamma rays and neutrons and their various units of dosage measurement, the *roentgen*, the *rep* (roentgen equivalent, physical), the *rad* (radiation absorbed dose) and the *rem* (roentgen equivalent, man).

Biological damage from high energy radiation is due to the heavy ionization produced. The most serious effect is damage to the nucleic acids and nucleoproteins that contain the coded information in the genes. In germ cells this may produce genetic mutations that can be handed on to future generations; in somatic cells it may result in abnormal change or death when the cell attempts its next division. Thus actively proliferating tissues such as bone marrow, lymph nodes, thymus, intestinal mucosa, skin and hair follicles are particularly radiosensitive. Acute clinical symptoms usually appear after a dose of 100 to 200 rads. The dose for 50% lethality in man is about 400 to 500 rads, in which range death is usually due to marrow and lymphopoietic destruction. At higher doses death may result from intestinal tract damage, and at very high doses, changes produced in the central nervous system are rapidly fatal. The effects of chronic exposure to low levels of radiation are more difficult to define; they tend to be cumulative, though with a certain degree of potential recovery. There is considerable evidence to indicate that they include premature ageing, decreased life span, and increased incidence of certain malignancies and leukemia. Though there is no question that radiation causes damage, there is a raging controversy regarding the effect of very low doses and whether or not any threshold exists below which no significant radiation injury is produced. At present it seems impossible to resolve this argument. In general there is a tendency to adopt the more cautious view, for the present at least, and consider any increase in radiation exposure undesirable.

Regarding the matter of safety standards, Dr. Copp observed that every time the ICRP or comparable bodies meet to re-appraise the matter of "maximum permissible radiation dosage" the upper limit of such dosage is lowered. To remove the implication that this dosage is authoritatively acceptable, it has been suggested that the term "Maximum Permissible Dose" be changed to "Radiation Protection Guide Level".

In Canada many sources contribute to the radiation received each year by our citizens. Important among these is the natural background radiation that has existed since the beginning of time. Compared with this, the radiation received from fallout in most areas is relatively small. The most pessimistic have estimated that radioactive fallout from bomb tests as conducted in recent years may cause one to eight more cases of leukemia and bone cancer per year in Canada. There is much more cause for concern about bomb *using* than about bomb *testing*. In Canada the record of occupational exposure to ionizing radiation is, in general, a very good one, particularly so in the atomic power industry, despite its peculiar hazards. The most important source of exposure involves the use of radiation in medical practice, which in our western society may approximate the annual radiation dose from natural background sources. The medical profession in general, and radiologists in particular, have the most to contribute in reducing this exposure by every possible, logical means, weighing the risks of every procedure entailing such exposure against the benefit to the patient.

Dr. R. M. Taylor, Executive Director of the National Cancer Institute of Canada, discussed the immediate and delayed somatic effects of ionizing radiation. *Acute radiation sickness* is characterized by nausea and vomiting, fever, epilation and hematopoietic damage. The latter is reflected in early lymphopenia, transient leukocytosis with subsequent leukopenia, and thrombocytopenia. If the patient survives, the various hematological elements gradually return to normal. Though the $L.D._{50}$ is generally considered to lie within the range of 350 to 450 rads for humans, one child treated for leukemia at the Princess Margaret Hospital, Toronto, survived exposure to 850 rads of whole body radiation combined with fetal liver marrow transplantation.

In considering the *delayed somatic effects* of radiation exposure, Dr. Taylor pointed out that the death rate from *leukemia* has shown a steady increase in recent years, in Canada as in other countries, and there is good evidence that this is related, in part at least, to increasing exposure to ionizing radiation. Leukemia mortality in Canadian males, for example, was 3.5 per

100,000 in 1941 and 6.5 per 100,000 in 1958. At doses above 200 rads there is a linear relationship between radiation dosage and leukemia incidence. Below this dose level there is no evidence of such a relationship, but until conclusive information is available it is probably wise to assume that a linear relation does exist at lower dose levels as well and that there is no threshold below which radiation induces no leukemogenic effect. *Radiation dermatitis* is a well-recognized and distressing long-term hazard of exposure. *Thyroid carcinoma* has been reported as a late effect of thyroid radiation in children receiving over 200 rads, but there is no evidence of an increase in thyroid cancer in adult age groups despite the wide use of thyroid radiation in the treatment of thyrotoxicosis with radioactive iodine. *Bone cancer* as a late radiation effect has been most prominent among dial painters exposed to internal radiation. Here, the latent period as a rule is 15 years or more and the critical dose appears to be in the vicinity of 1000 rads. The old story of the *lung cancers* of workers in the Schneeberg and Joachimstahl mines exposed to radon gas is well known and oft repeated. On the average, those so affected had a 17-year history of such exposure entailing doses to the bronchial epithelium that ranged from 1000 to 10,000 rads. *Post-radiation cataracts* may occur with latent periods following exposure, varying from a few months to five years. The lens is the most vulnerable component of the ocular apparatus to the effects of radiation which cause sufficient damage to its epithelium to result in cataracts, above a threshold of approximately 600 rads. *Radiation pneumonitis* results from doses in the vicinity of 2000 rads and may not become evident for several years after exposure. The early inflammatory changes are followed by fibrosis in alveolar walls, hyaline membrane formation in alveolar spaces, fibrinous exudate and interstitial fibrosis. *Radiation nephropathy* may also occur as a delayed effect of exposure, presenting a clinical picture that may resemble acute or chronic nephritis, essential or malignant hypertensive nephropathy, which may eventuate in recovery or death. Among the pathological features of this lesion is a smudgy eosinophilic necrotic swelling of the arterioles in afferent glomerular loops. This complication is important to recognize because if only one kidney is affected, the condition may be cured by nephrectomy. *Sterility,* another long-term hazard, may be permanent after gonadal exposures of about 500 rads in the male and 800 rads in the female. *Decreased life span* as a result of radiation exposure has been reported on the basis of animal studies. To date there are no reliable data relative to humans in this regard.

The ICRP has recommended a limit of 5 rem per year as the so-called "safe" level of exposure for occupationally exposed personnel. Dr. Taylor observed that it is unlikely that a total lifetime exposure to ionizing radiation up to 200 rem would cause any serious effects or that exposure to a total of 50 rem over a period of 30 years would produce any significant genetic effect.

Dr. F. Clarke Fraser, Professor of Genetics at McGill University, in discussing the genetic implications of irradiation for Canadians, defined the gene as the code or blueprint that guides our development and function, acting through its control of the specificities of large molecules such as those of hemoglobin, enzymes or antigens. Hereditary diseases are caused by genes that have been altered in such a way that they do not perform their normal function, this alteration being known as a mutation. Mutations lead to changes in protein structure that may, among many other effects, result in conditions such as sickle cell disease (abnormal globin structure), inborn errors of metabolism (phenylketonuria, albinism or galactosemia, for example), and certain types of malformation. Owing to the fact that we still know so little about factors that determine the frequencies of mutant genes in the population, it is impossible to make precise statements about the genetic effects of radiation in man. Radiation results in genetic mutations by its effect on the desoxyribonucleic acid content of genes. According to United Nations figures, we now receive a *"genetic" dose* of 3 rem per 30 years from background radiation, 0.5 to 5 rem per 30 years from medical and industrial sources, and 0.01 to 0.1 rem per 30 years from fallout. A recent British survey indicates that the citizen in that country receives an average *"genetic" dose* of 20 mr per year or 0.6 mr over 30 years. In the United States this exposure is probably higher. In Britain it is estimated that 5% of the annual *genetic dose* is contributed by chest radiography, one-third by obstetric radiology, one-third by radiography of the pelvis and femur and a mere 1/1000 from mass miniature and dental x-rays. It was considered that *genetic doses* from medical radiography could probably be reduced by about one-third by more careful techniques. Applying the genetic effects of these British data to Canada, such radiation exposure of the general population could be expected to result in new mutations after one generation that would account for one achondroplastic every five years, 16 persons with gross physical or mental defects per year, and a total of 125 genetic deaths per year. In addition there would be unknown effects on I.Q., longevity and vitality and possible influences on the incidence of leukemia, bone malignancy and malformations that could not be predicted in the light of present knowledge. In conclusion, Dr. Fraser expressed the opinion that exposure to ionizing radiation, though medically beneficial now, is certainly genetically bad for the future, that there is no such thing as a *safe* dose from the genetic viewpoint, and that with current practices man is doing things to his genetic structure that should be causing him more worry. Genetic effects of radiation are cumulative and irreversible and it becomes a matter of balancing the present benefits against possible ill effects in the future, in deciding the proper place of medical radiation. Certainly, all *unnecessary* exposure should be avoided.

Dr. C. G. Stewart, Director of the Medical Divison of Atomic Energy of Canada, Ltd., discussed three of the sources of ionizing radiation for which man himself is responsible: the radiation from nuclear reactors, from artificial radioactive substances used in industry and medicine, and from radioactive waste materials. All of these involve the physical process of fission, the edifice on which the nuclear energy industry is built. While the potential hazard to the public of nuclear reactor operations is tremendous, Dr. Stewart stressed that it remains but a potential one which is being well and adequately controlled by extensive and expensive measures to protect the environment from the accidental release of radioactivity. The hazards to man associated with reactors are controlled principally by (1) design and operation of the reactor in such a

manner that accidental release of its core content is virtually impossible and (2) a well-organized radiation protection system to guard the individual worker from exposure during normal and abnormal operation. Disposal of radioactive fission products of reactor operations constitutes a further massive and steadily growing problem in protection. Essentially, disposal and dispersal of radioactive wastes is arranged so that the rate of release of specific radionuclides is such that their concentration in the environment to which the public is exposed is within the range considered "safe" by the ICRP and within the regulations of the Atomic Energy Control Act of Canada. In concluding, Dr. Stewart noted that large reactors have now been operated at Chalk River for over 12 years without a single lost-time accident among employees due to radiation overexposure and with no damage to the public domain. He observed that Canada's experience is in keeping with the statement of the U.S. National Academy of Sciences – National Research Council 1960 Report on the Disposal of Radioactive Wastes: "There does not appear to be anything inherent in the overall waste control problem that need retard the development of the nuclear energy industry, at the same time assuring adequate protection of public health and safety." The price tag attached to this conclusion will be the cost of the continuing scientific and engineering research necessary to ensure the maintenance of safety standards – plus eternal vigilance.

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The candidates whose names are listed below were successful in the 1960 Certification examinations in the specialties of Pathology, Physical Medicine and Rehabilitation, Psychiatry, Public Health, and Diagnostic Radiology.

SPECIALTY OF PATHOLOGY (25)

ARNOTT, JANET ELIZABETH M.B., B.S.(London) 1953	Department of Pathology, Winnipeg General Hospital, Winnipeg, Man.
BELL, HAROLD EDWIN M.D.(Alberta) 1949	11119–71 Avenue, Edmonton, Alta.
BIRSE, SHEILA HAMILTON M.B., Ch.B.(Edinburgh) 1952	996 Danforth Road, Scarborough, Ont.
CARRUTHERS, JOHN SCOTT M.D.(Western Ontario) 1955	92 Otter Crescent, Toronto 12, Ont.
CONEN, PATRICK EDWARD M.B., B.S.(London) 1951	31 Alexander Street, Toronto 5, Ont.
FATTAL, GARABED ABDULLAH M.D.(French Faculty of Medicine, Beirut) 1953	Department of Pathology, University Hospital, Saskatoon, Sask.
GAGNON, PAUL MAURICE M.D.(Laval) 1951	972, rue Brown, Quebec 6, Que.
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HENDRY, JAMES M.B., Ch.B.(Aberdeen) 1947	The Laboratory, Brandon General Hospital, Brandon, Man.
HORNE, WILLIAM IAN M.B., Ch.B.(Aberdeen) 1950	280–9th Avenue N.W., Swift Current, Sask.
KERENYI, NORBERT ANDREW M.D.(Budapest Medical University) 1952	Pathological Institute, 62 University Avenue, Halifax, N.S.
LAUGHLAN, STUART CAMPBELL M.B., Ch.B.(Edinburgh) 1954	General Hospital, St. John's, Nfld.
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MACCONNACHIE, HUGH FRASER M.B., Ch.B.(Edinburgh) 1952	4266 Old Orchard, Apt. 8, Montreal, Que.
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O'BRIEN, FREDERICK FRANCIS M.D.(Ottawa) 1955	St. Joseph's Hospital, Sarnia, Ont.
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WYLLIE, JOHN CLIFTON M.D., C.M.(Queen's) 1952	Department of Virology, Hospital for Sick Children, 555 University Avenue, Toronto 2, Ont.

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BASHOW, LYNN ELWYN M.D., C.M.(Dalhousie) 1943	Forest Hill Rehabilitation Centre Inc., P.O. Box 265, Fredericton, N.B.
BLAIR, DAVID CROW M.D., C.M.(McGill) 1952	115 Torbarrie Road, Downsview, Ont.
BROOKS, DAVID HALL B.M., B.Ch.(Oxon.) 1946	Officers' Mess, R.C.A.F. Station, Rockcliffe, Ont.
GUIMOND, RÉMI M.D.(Laval) 1955	241, rue Tessier, Chicoutimi, Que.

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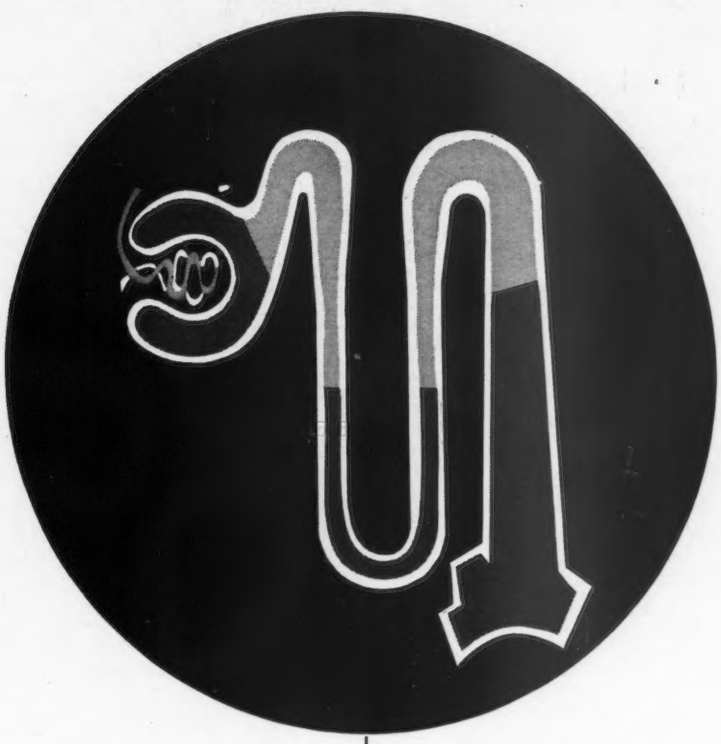

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CREAMER, ALICE MARY M.B., B.Ch.(Dublin) 1942	Assistant Clinical Director, Provincial Mental Hospital, Essondale, B.C.
CUMBERLAND, JUNE ROSAMOND M.B., Ch.B.(Liverpool) 1952	The Montreal Children's Hospital, 2300 Tupper St., Montreal, Que.
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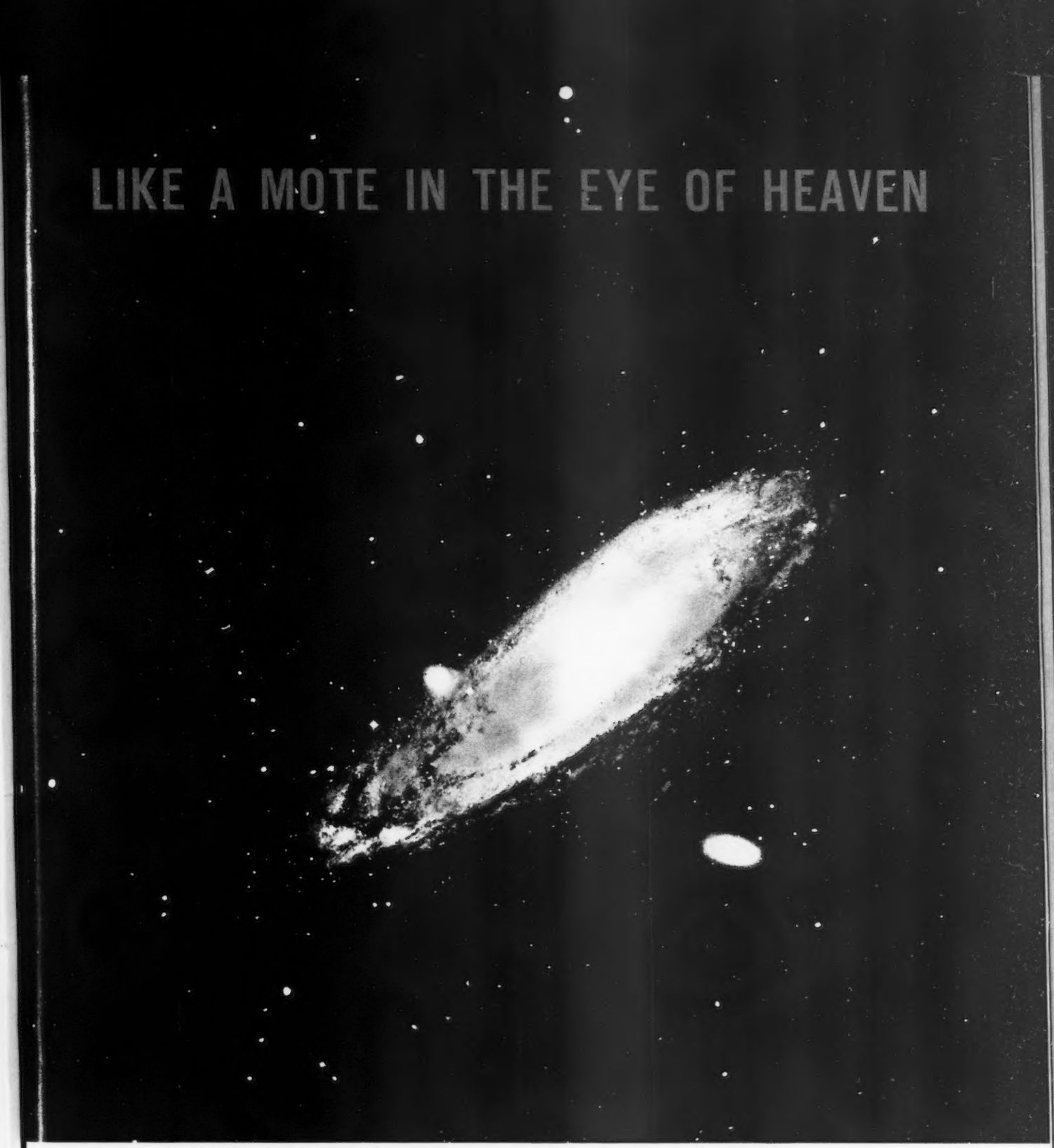
MILLER, MARVIN EARL M.D.(Toronto) 1955	14 Balaby Crescent, Don Mills, Ont.
MOORE, MAURICE BENN M.B., B.S.(Durham) 1946	Box 1000, Ponoka, Alta.
MULLER, HERBERT FRIEDRICH J. M.D.(Cologne) 1941	418 Pine Avenue West, Montreal, Que.
NICHOL, HAMISH M.B., B.Chir.(Cantab.) 1952	2444 Bouck Avenue, New York 69, N.Y., U.S.A.
PARKINSON, RAYMOND M.D.(British Columbia) 1954	4375 Halley Avenue, South Burnaby, B.C.
PLANTE, NORMAND M.D.(Laval) 1956	610 est, rue Godbout, apt. 4, Quebec 3, Que.
RADO, EVA M.D.(Manitoba) 1956	Nova Scotia Hospital Department of Psychiatry, Woodside, N.S.
ROPER, PETER DIGBY LEWINGTON M.B., Ch.B.(Glasgow) 1951	Allan Memorial Institute, 1025 Pine Avenue West, Montreal 2, Que.
RUSSELL, AXEL M.D.(Graz, Austria) 1951	4014 Grey Avenue, N.D.G., Montreal, Que.
RYAN, EDMOND M.B., B.Ch.(National Univ., Ireland) 1952	Department of Health, Hospital for Mental and Nervous Diseases, St. John's, Nfld.
MORIN, GASTON DONATIEN M.D.(Montreal) 1951	2405 Clementine Boulevard, Ottawa 1, Ont.
SAASK, LINDA M.D.(Eberhard-Karls, Tübingen, Germany) 1946	The Ontario Hospital, 999 Queen Street West, Toronto, Ont.
SAINT-LAURENT, CLAUDE M.D.(Laval) 1955	827 North 63rd Street, Philadelphia 31, Pa., U.S.A.
SCHMIDT-MALO, HILDEGARD JOHANNA M.D.(Breslau, Germany) 1941	31 Alexander St., Apt. 815, Toronto 5, Ont.
SCHOFIELD, THOMAS EDWARD M.D.(Toronto) 1949	4 Stamford Square North, Scarborough, Ont.
SCOTT, FLORA M.D.(Alberta) 1954	813 Downland Avenue, New Sudbury, Ont.
SLAKOV, ROY ISRAEL M.D.(Oregon) 1953	Birks Building, Room 929, 718 Granville Street, Vancouver 2, B.C.
SMITH, RONALD MURRAY, M.D.(Western Ontario) 1949	Drummond Medical Building, 1414 Drummond Street, Montreal, Que.

(Continued on page 511)

LIKE A MOTE IN THE EYE OF HEAVEN



In theory, the chance of a single bacteria developing resistance to two antibiotics simultaneously is extremely small: only 1 in 10 quadrillion.* In an effort to approximate the results of practical experience to those attainable in theory, authorities in antibiotic therapy are recommending full doses of two unrelated antibiotics as the best method for delaying or preventing resistance. Albamycin and tetracycline are frequently prescribed together for this reason, and many physicians prefer to specify Albamycin T, a 1:1 ratio of both drugs.

*For an idea of the magnitude of 10 quadrillion, imagine all the stars in 200,000 Milky Ways.

Albamycin*T

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*REGISTERED TRADEMARK

Upjohn

sustained steroid absorption on reduced dosage

Medrol® Medules†

(Continued from page 508)

STACEY, DONALD LESLIE M.D., C.M.(Dalhousie) 1956	Nova Scotia Hospital, Dartmouth, N.S.
SUMMERBY, JOHN HALL M.D., C.M.(McGill) 1951	Westminster Hospital, D.V.A., London, Ont.
THOMPSON, JAMES M.B., B.Ch., B.A.O. (Queen's, Belfast) 1951	Provincial Mental Hospital, Ponoka, Alta.
TYHURST, LIBUSE M.D.(Charles Univ., Prague, Czechoslovakia) 1954	5687 College High Road, Vancouver, B.C.
VERHULST, JAN M.D.(Leiden, Holland) 1949	1 Daleena Drive, Don Mills, Ont.
WARD, THOMAS FRANCIS M.D.(Toronto) 1954	Thistletown Hospital Thistletown, Ont.

SPECIALTY OF PUBLIC HEALTH (1)

NORTHOVER, ROBERT JOHN M.D.(Toronto) 1940	242 Kraft Road, Fort Erie, Ont.

SPECIALTY OF DIAGNOSTIC RADIOLOGY (40)

AWERBUCK, BERNARD M.D.(Toronto) 1954	3638 Bathurst St., Apt. 408, Toronto 19, Ont.
BLACKBURN, ROBERT M.D.(Laval) 1953	1385, rue Portland, Sherbrooke, Que.
BLOOMFIELD, MICHAEL ANTHONY M.B., Ch.B.(Manchester) 1954	Ridout Towers, Apt. 606, 100 Ridout Street South, London, Ont.
BOCIEK, ROBERT CARL M.D.(Ottawa) 1955	17 Labelle Avenue, Sault Ste. Marie, Ont.
BRAY, GORDON M.D.(Toronto) 1949	1502 Wiggins Avenue, Saskatoon, Sask.
BRIGGS, JAMES ALLEN DOUGLAS M.B., B.Chir.(Cambridge) 1953	Radiology Department, Sunnybrook Hospital, Toronto 12, Ont.
CLEGHORN, GORDON MURRAY M.D.(Manitoba) 1955	Radiology Department, St. Boniface Hospital, St. Boniface, Man.
CRANG, DONALD FRANK M.D.(Western Ontario) 1953	155 Kingsmount Boulevard, Sudbury, Ont.
CULLEN, PHILLIP JOHN M.D.(Toronto) 1952	119 Riverside Drive, Sudbury, Ont.
DESLAURIES, GABRIEL M.D. (Montreal) 1950	790 St-Louis, Ville St-Joseph, St-Hyacinthe, Que.
DWYER, JOSEPH MORAN M.D.(Ottawa) 1955	St. David's, Ont.
ELDER, ARTHUR MALCOLM M.D.(Toronto) 1954	56 Somerdale Square, Guildwood Village, Scarborough, Ont.
EVANS, BARRY VICTOR M.D.(Manitoba) 1955	14338 Park Drive, Edmonton, Alta.
FEORE, THOMAS DERMOT RYAN M.B., B.Ch.(National Univ., Ireland) 1955	Department of Radiology, Ottawa General Hospital, Ottawa, Ont.
FLOOD, HENRY JOSEPH M.D., C.M.(McGill) 1955	Department of Diagnostic Radiology, Saint John General Hospital, Saint John, N.B.
FREEDMAN, RALPH EDWARD M.D.(Toronto) 1955	1967 Victoria Park, Avenue Scarborough, Ont.
FRIEND, WILLIAM DONALD M.D.(Toronto) 1952	357 Boler Road, Byron, Ont.
GAGNON, ROBERT FÉLIX M.D.(Laval) 1950	27, rue Martin, Riviere-du-Loup, Que.
GEORGE, JAMES ALEXANDER M.D., C.M.(McGill) 1949	216 Dunvegan Road, Toronto 7, Ont.
GIBSON, JOHN DOUGLAS M.D.(Toronto) 1954	74 Colin Avenue, Toronto 7, Ont.
GRANTMYRE, EDWARD BARTLETT M.D., C.M.(Dalhousie) 1956	11 Westgate Drive, Armdale, Halifax Co., N.S.
GUNN, DACIE M.D., C.M.(McGill) 1945	Deer Lake Drive, North Burnaby, B.C.
HENDIN, IRVINE DONALD M.D.(Manitoba) 1956	14922—84th Avenue, Edmonton, Alta.
HILL, ROSS OGILVIE M.D., C.M.(McGill) 1948	4545 Royal Avenue, Montreal 28, Que.
HORNE, SCHARLEY-MAY GARRARD M.D.(Toronto) 1953	48 Eccleston Drive, Apt. 215, Toronto 16, Ont.
JAMISON, CLARENCE ARNOLD M.D.(Alberta) 1942	3994 West 35th Avenue, Vancouver 13, B.C.
LEGER, LÉO PAUL ERIC JOSEPH M.D.(Laval) 1951	11853, Michel Sarrazin, Apt. 5, Montreal 9, Que.
LINSDELL, FRANCIS JAMES M.D.(Western Ontario) 1952	100 Ridout Street South, Apt. 500, London, Ont.
LUKAS, WILLIAM JULIUS M.D.(Budapest) 1952	Notre Dame Hospital, North Battleford, Sask.
LUSSIER, GISÈLE M.D.(Montreal) 1956	20, avenue Elmwood, Outremont, Montreal, Que.
LYNCH, JOHN M.B., B.Ch.(National Univ., Ireland) 1951	Department of Radiology, Montreal Children's Hosp., 2300 Tupper Street, Montreal, Que.
MACDONALD, DOREEN ISOBEL M.D.(Toronto) 1950	854 Chriseden Drive, Port Credit, Ont.
MACDONALD, JOHN CAMERON M.D., C.M.(Dalhousie) 1951	266 Rossini Boulevard, Windsor, Ont.
MERRIAM, RICHARD KERR M.D., C.M.(Dalhousie) 1952	Drawer 608, Red Deer, Alta.
OLACKE, FRANK ALBERT M.D.(Manitoba) 1940	Vancouver General Hospital, Vancouver, B.C.
OSZADSZKY, SANDOR M.D.(Budapest) 1951	Department of Radiology, St. Mary's Hospital, 3830 Lacombe Avenue, Montreal, Que.
ROY, CLAUDE M.D.(Laval) 1956	3275, avenue Royale, Giffard, Quebec 5, Que.
SHANNON, MALCOLM PARRY L.R.C.P., L.R.C.S. (Edinburgh) 1951	Department of Radiology, Victoria Public Hospital, Fredericton, N.B.
STEINHARDT, MARVIN IRWIN M.D.(Bern, Switzerland) 1955	2515 Bathurst Street, Toronto, Ont.
WOOD, BETTY JOAN M.D.(Manitoba) 1954	The University Hospital, Edmonton, Alta.

CHANGE OF ADDRESS

Subscribers should notify the Canadian Medical Association of their change of address one month before the date on which it becomes effective, in order that they may receive the Journal without interruption. The coupon on page 45 is for your convenience.

Canad. M. A. J.
Mar. 4, 1961, vol. 84

GENERAL PRACTICE

COLLEGE OF GENERAL PRACTICE OF CANADA AN INVITATION TO VANCOUVER!

SCHEDULE OF EVENTS — 1961 SCIENTIFIC ASSEMBLY

Friday, March 24

2.00 p.m. Executive meeting, Salon E, Hotel Vancouver
8.00 p.m. Buffet Dinner for Board of Representatives at the residence of Dr. E. C. McCoy, 5358 Angus Drive, Vancouver

Saturday, March 25

9.00 a.m. Board of Representatives meeting, Board Room, Hotel Vancouver
Also convening at 2.00 p.m. and 8.00 p.m. in Board Room

Sunday, March 26

9.00 a.m. Board of Representatives meeting, Board Room, Hotel Vancouver
Also convening at 2.00 p.m. in Board Room
7.00 p.m. Registration, 1st Floor, Hotel Vancouver
8.00 p.m. President's Reception, Banquet Room and Lounge, Hotel Vancouver

Monday, March 27

7.45 a.m. Breakfast meeting, Chairmen of sessions
8.30 a.m. Doctors' Registration, Queen Elizabeth Theatre
9.00 a.m. Scientific sessions, Queen Elizabeth Theatre
9.30 a.m. Ladies' Registration, 1st Floor, Hotel Vancouver
Ladies' Hospitality Room, Salon D, Hotel Vancouver
12.15 p.m. Luncheon, Ballroom, Hotel Vancouver—Guest speaker Dr. J. G. Walsh, President, American Academy of General Practice
2.00 p.m. Scientific sessions, Queen Elizabeth Theatre
3.00 p.m. Ladies' Fashion Show and Tea, Panorama Room, Roof of Hotel Vancouver
7.45 p.m. B.C. Chapter meeting, East Lower Lobby, Queen Elizabeth Theatre
9.00 p.m. B.C. Section of General Practice meeting, East Lower Lobby, Queen Elizabeth Theatre

Tuesday, March 28

8.30 a.m. Doctors' Registration, Queen Elizabeth Theatre
9.00 a.m. Scientific sessions, Queen Elizabeth Theatre
9.30 a.m. Ladies' Registration and Hospitality Room, Salon D, Hotel Vancouver
12.15 p.m. Luncheon for Board of Representatives and Medical Directors of pharmaceutical firms, Salon B, Hotel Vancouver
2.00 p.m. Annual General Meeting, Queen Elizabeth Theatre
7.30 p.m. Dinner and entertainment, Chinatown

Wednesday, March 29

8.30 a.m. Doctors' Registration, Queen Elizabeth Theatre
9.00 a.m. Scientific sessions, Queen Elizabeth Theatre
9.30 a.m. Ladies' Registration and Hospitality Room, Salon D, Hotel Vancouver
11.30 a.m. Ladies' Brunch—Shaughnessy Golf Club, followed by tour of City
12.15 p.m. Luncheon, Banquet Room, Hotel Vancouver—Guest speaker Dr. R. MacGregor Parsons, President, Canadian Medical Association
2.00 p.m. Board of Representatives meeting, Board Room, Hotel Vancouver
2.00 p.m. Scientific sessions, Queen Elizabeth Theatre
6.30 p.m. Annual Dinner and Dance—Ballroom, Lounge and Banquet Room, Hotel Vancouver

Thursday, March 30

8.30 a.m. Doctors' Registration, Queen Elizabeth Theatre
9.00 a.m. Scientific sessions, Queen Elizabeth Theatre
9.30 a.m. Executive meeting, Hotel Vancouver
12.15 p.m. Buffet luncheon for Board of Representatives and Press, Hotel Vancouver
2.00 p.m. Scientific sessions, Queen Elizabeth Theatre

ASSOCIATION NOTES

FILM SHOWINGS AT THE ANNUAL MEETING

A three-day showing of medical films is planned for the 94th Annual Meeting of the C.M.A. in Montreal, June 19-23. The organization committee is very anxious to show modern teaching films covering every aspect of medical science. Films which demonstrate methods would be particularly welcome. Those who have such films and are prepared to lend them for exhibition at the meeting are asked to write directly to Dr. T. Primrose, Royal Victoria Hospital, Montreal, giving particulars of the subject matter, size and length of showing. The deadline for acceptance of films is April 15.

Canad. M. A. J.
Mar. 4, 1961, vol. 84

BOOK REVIEWS

BLOOD DISEASES OF INFANCY AND CHILDHOOD. Carl H. Smith. 572 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1960. $17.00.

It is many years since the publication of a textbook of pediatric hematology, and this comprehensive volume will provide a valuable reference work for all medical libraries. Although the author has addressed the book to medical students and practitioners, it may well be that hematologists will find it especially useful.

The entire subject matter of hematology is touched upon, but the emphasis is on those matters that are of greatest importance in the growing child. The first half of the book is devoted to the red cell, the blood changes during growth, blood dyscrasias in relation to fetal-maternal interaction, and the anemias. The chapter on neonatal jaundice, which includes the recent knowledge of bilirubin metabolism, serves as a good introduction to the two chapters on hemolytic disease of the newborn. Other sections deal with the hypoplastic anemias, hemolytic anemias, and the hereditary hemoglobinopathies. These are followed by chapters on the leukocytes, leukopenic syndromes, and the leukemias. Coagulation, and its deficiencies, the hemophilias, are considered in great detail, incorporating discussions of hemophilia B (Christmas disease) and related conditions. Finally, there is a chapter on the purpuras.

The book is essentially a clinical one, but the basic physiology is presented, and there are sections on morphology where appropriate. The illustrations are mainly black-and-white photomicrographs and are reproduced clearly. The book however is in no sense an atlas of hematology. Special laboratory techniques, e.g. the thromboplastin generation test, are described in the appropriate chapter, rather than being arranged in a section on techniques. Complete bibliographies are appended to each chapter.

This book is most welcome, and is recommended particularly to hematologists and pediatricians.

SHAW'S TEXTBOOK OF OPERATIVE GYNECOLOGY. Revised by John Howkins, Obstetrical and Gynecological Surgeon, St. Bartholomew's Hospital, London, Eng. 484 pp. Illust. 2nd ed. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1960. $18.00.

In his preface to the second edition Mr. Howkins pays a well-deserved tribute to the late British gynecologist, Wilfred Shaw, who wrote the original edition of this textbook. Howkins' motivation in writing this second edition is best illustrated by his own words. "In deletion and addition it was my purpose to produce a textbook of gynecological surgery where the emphasis lay in standard, orthodox and accepted British practice, so that the apprentice surgeon should find guidance and help in the choice and performance of his operations."

There can be no doubt that he has succeeded admirably in his stated purpose. He has produced a most readable book; well and extensively illustrated, with concise, clear descriptions of operative procedures and brief but usually adequate comments on most of the common gynecological problems. Generally speaking, Canadian opinion and practice will agree with Mr. Howkins' views, although it is inevitable that many minor differences will exist. His attitudes on the subjects of total hysterectomy, conservation of ovarian tissue, backache in women, preoperative use of intrauterine radium in carcinoma of the fundus and the vexing problem of carcinoma-in-situ, for example, would receive much support in this country.

It is rather surprising to find so much space devoted to the Shauta operation (with 14 excellent, almost full-page drawings), as this method of treatment of cancer of the cervix could hardly be called "standard, orthodox and accepted British practice". His explanation seems not unreasonable. "As an anatomical exercise in vaginal surgery it is of great value, and for this reason alone its inclusion in the text is justified." Perhaps such exercise was the object of his "synchronous combined abdomino-vaginal hysterectomy" (*Lancet*, 1: 872, 1951); this may represent a major advance for those patients with cervical cancer who require radical surgery instead of radiation.

In cases of endometrial carcinoma he emphasizes the importance of knowing the exact location and extent of the lesion. He describes in detail his method of fractional curettage. This would eliminate inadequate surgical measures for those women with endometrial cancer involving the cervix.

When the reader may find the deliberate brevity of the text insufficient for his needs, Mr. Howkins has provided extensive references at the end of each chapter. This is a good book and should receive wide acceptance.

EMOTIONAL MATURITY. The Development and Dynamics of Personality. Leon Saul. 2nd ed. 393 pp. Illust. J. B. Lippincott Company, Montreal, 1960. $6.50.

Many who believe in the doctrines of Freud insist that all behaviour, sick or otherwise, can be explained, and that only the followers of the father of psychoanalysis have the true explanation. Yet psychoanalysts often state their views poorly. In this book the author tries to present his interpretation of Freud's theories in a form which would be useful to an audience with diverse backgrounds; he only partly succeeds. He pictures emotional maturity as an idealized goal towards which we struggle. The mature person could enjoy life, control his aggressions, and have a socially acceptable sexual adjustment. Unfortunately, we never quite reach this ideal state because a counterforce impedes our development and sometimes makes us regress to immature behaviour. This regressive force is a pattern of emotional insecurity imprinted during the first six years of life. Neurotic disorders are a replay of this early theme.

The author believes that the anxious parent condemns his child to develop neurosis in adult life by mishandling the infant's dependent state. It is a question of timing—he is thrust out of the protective nest either too early or too late. He contends that proper child-rearing practices are needed to prevent the neuroses which result from immaturity.

While free from jargon, the book is loosely constructed and unevenly written. It is a useful presentation of Dr. Saul's view of psychoanalysis but would have been much more useful had it been shorter and better written.

(Continued on page 517)

(Continued from page 514)

RYPINS' MEDICAL LICENSURE EXAMINATIONS. Prepared under the editorial direction of Walter L. Bierring. 805 pp. 9th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1960. $11.00.

The ninth edition of this book has been prepared by a representative committee under the editorial direction of Dr. Walter Bierring, whose professional status and experience as a former member of the National Board of Medical Examiners (U.S.A.) and of the American Board of Internal Medicine render him eminently suited for the task.

The book should prove useful to the student preparing for board examinations, particularly for one who is not a recent graduate, consisting as it does of sections on anatomy, physiology, biochemistry, microbiology; pathology and pharmacology in the preclinical portion, and in the clinical sciences, of sections on internal medicine, surgery, obstetrics and gynecology, preventive medicine and public health, and psychiatry. While these sections do not attempt to replace the accepted textbooks on the various subjects, yet they give a good summary, which should be useful in reviewing the particular subject. At the end of each section a set of questions is appended to test the knowledge of the student and give him practice in writing an answer.

The editor has added a section on the general philosophy of examinations in which he describes and discusses the merits of the various types of examinations, such as the essay question, the multiple-choice question, and oral and practical examinations. Questions representative of each type are used for illustration.

This book will be of interest to those who have to conduct examinations in medical subjects, to those who conduct so-called "quiz" courses, and particularly to the candidate who wishes to brush up before sitting for the board examinations. While it is based on board examinations in the United States, it will be equally useful for those preparing for the examinations of the Medical Council of Canada or those of the various provincial licensing bodies.

ENDEMIC GOITRE. World Health Organization Monograph Series No. 44. 471 pp. Illust. French and Spanish editions in preparation. World Health Organization, Geneva, Switzerland, 1960. $8.00.

This World Health Organization monograph results from the world-wide interest in and study of endemic goitre that was initiated in 1950 by that organization. The list of contributors is international in scope, which makes the over 2000 references quoted particularly valuable. All aspects of endemic goitre are discussed, including its history, prevalence, etiology and pathology. The results of demographic surveys and problems of goitre control are also presented. It is interesting to note that Canada was one of the first countries to introduce compulsory legislation relative to iodized salt and how few countries have such legislation. Since it is a decade since this legislation was introduced, Canadians should now attempt to assess its efficacy.

Certainly, this monograph fulfils its task of rendering "a useful service to public health workers, as well as all those engaged in the study of goitre, by inviting well-known goitre workers to prepare reviews covering all aspects of the subject". While its contents are of relatively specialized interest for the general physician, all those interested in the problem of goitre and all medical libraries should provide themselves with this invaluable reference book.

PRINCIPLE OF BONE X-RAY DIAGNOSIS. George Simon, London. 170 pp. Illust. Butterworth & Co. (Publishers) Ltd., London; Butterworth & Co. (Canada) Ltd., Toronto, 1960. $11.50.

Although this book has been written primarily for radiologists, it is one that no surgeon dealing with orthopedic conditions will wish to be without. The author has classified his material into groups based on similarities of radiographic appearance, and where a definitive diagnosis is not possible on x-ray appearance alone, has pointed out further investigations that might prove helpful.

Throughout the book, the radiographic picture has been correlated with clinical details, pointing out how important this correlation is to rational radiologic diagnosis. It is well illustrated and pleasingly concise, presenting an enormous amount of material with little or no padding.

One section deals with alterations in bone shape, while another deals with alterations in the position of a bone. The section on increased bone density has been divided into passages dealing with generalized increases and localized increases, and there is a similar section on decreased bone density. There are chapters on alterations in the appearance of epiphyses, single and multiple, as well as discussions of poorly demarcated and well-demarcated erosions of the surface of a bone.

This book fills a real need, and as an aid in radiologic diagnosis it is likely to become a classic in its field.

TREATMENT OF CANCER AND ALLIED DISEASES. Vol. 4, Tumors of the Breast, Chest, and Esophagus. 2nd ed. Edited by George T. Pack and Irving M. Ariel. 655 pp. Illust. Paul B. Hoeber Inc., Medical Book Department of Harper & Brothers, New York, 1960. $30.00.

This is a massive reference work by 70 authors. Each presents his own ideas of therapy as supported by personal experience. Radiotherapists and surgeons are given equal opportunity to advocate their own methods of treatment. The overall effect is one of objectivity; the reader can study the alternatives and make his own choice. The whole book is generously illustrated with photographs and documented by tables; almost all operative procedures and many radiotherapeutic techniques are clarified by diagrams. An extensive bibliography is arranged by chapters at the back of the book. This work is of great value and the editors are to be congratulated for their efforts in bring together the combined experience of many experts.

THE ALCOHOL PSYCHOSES. Demographic Aspects at Midcentury in New York State. Benjamin Malzberg. 46 pp. Yale Center of Alcohol Studies, New Haven, Conn., 1960. $2.00.

This booklet is a statistical report. It contains concise comments on the numerous tables reported. There are 32 tables of figures supplying statistical information under 16 headings. This review considers first admissions to mental hospitals in the State of New York with diagnosis classed as Alcoholic Psychoses during the years 1948 to 1951.

The conclusions expressed in several sections are the opinions of the author and are not necessarily proved by the figures.

The work is of value for reference purposes. It is a worthwhile contribution to the field of alcoholism studies but of limited general interest.

UNTERSUCHUNG UND BEURTEILUNG DES HERZKRANKEN. H. W. Knipping, W. Bolt, H. Valentin and H. Venrath. 626 pp. Illust. Ferdinand Enke Verlag, Stuttgart, W. Germany, 1960. DM 93.

This is the second edition of this textbook from the University Clinic in Köln where the tradition in heart disease investigation goes back to Brown and Forsmann. In the preface the authors advocate that greater emphasis be placed on the prophylaxis of cardiac disease by means of physical-fitness programs and sports. This theme is frequently referred to throughout the book and is also advocated as a form of therapy.

The substance of the book is devoted to information required by a specialist in internal medicine who is entering the field of cardiac investigation and being involved in cardiac surgical procedures. The authors draw heavily from their experience with some 4000 cardiac catheterizations. The necessary diagnostic tests in both congenital and acquired heart disease are discussed and the usual findings of such investigations are presented. The lesions which are amenable to surgery are described and the usual complications of surgery are discussed from the diagnostic and therapeutic viewpoint. The chapter on diagnosis is weak in its presentation of auscultatory data. Another weakness is the tendency to classify the material presented in tabular form without explanation of the basis for such classifications. The chapter on the pulmonary pathophysiology of cardiac disease is superb and contains much information not to be found in other standard texts on this subject. It contains much original work from the authors' unit. The chapter on the use of radioactive isotopes in the diagnosis of cardiopulmonary disorders is also very good.

An appendix contains data on many of the most interesting patients from the authors' clinic, reflecting the completeness of their investigation. An extensive and quite up-to-date bibliography is included.

This is a detailed textbook on cardiac investigation which contains a great deal of information, especially in the field of cardiopulmonary physiology.

THE PERSON SYMBOL IN CLINICAL MEDICINE. Robert Cohn. 196 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $11.00.

This volume by Dr. Cohn contains a series of case histories, including all pertinent data of investigations, along with the graphic drawing of a person by the patient. This drawing is referred to as the person symbol. The case histories are illustrative of many problems in brain disorders. For those who have been using this technique a good deal over the last 10 to 15 years, the material may be of some interest. The book is not easy to read, and the reviewer does not believe that there is sufficient discussion of the theoretical basis of the concept of the person symbol. Each chapter should have included a suitable summary, the absence of which restricts the value of the book. Psychologists may possibly find it more valuable than neurologists or psychiatrists. The reviewer does not believe that it will be used much as a reference source.

PUBLIC HEALTH

SUMMARY OF REPORTED CASES OF NOTIFIABLE DISEASES IN CANADA*
ISSUED BY THE PUBLIC HEALTH SECTION, DOMINION BUREAU OF STATISTICS

Disease	*Week ended (1960)* Dec. 10	Dec. 17	Dec. 24	Dec. 31	*Cumulative total since beginning of year* 1960	1959
Brucellosis (Undulant fever) (044)	1	1	4	—	132	114
Diarrhea of the newborn, epidemic (764)	—	—	—	6	51	92
Diphtheria (055)	1	—	3	6	53	37
Dysentery: (045, 046, 048)	43	37	22	36	2,949	1,408
(a) Amebic (046)	1	—	—	1	5	2
(b) Bacillary (045)	40	19	22	11	2,313	1,228
(c) Other and unspecified (048)	2	18	—	24	631	178
Encephalitis, infectious (082.0)	—	—	—	—	9	23
Food poisoning: (049.0, 042.1, 049.2)	22	7	8	7	1,206	821
(a) Staphylococcus intoxication (049.0)	—	—	—	—	309	19
(b) Salmonella with food as vehicle of infection (042.1)	15	7	8	7	815	652
(c) Unspecified (049.2)	7	—	—	—	82	150
Hepatitis, infectious (including serum hepatitis) (092, N998.5)	196	231	175	173	6,247	4,715
Meningitis, viral or aseptic (080.2, 082.1)	16	13	18	8	630	936
Meningococcal infections (057)	2	—	3	3	151	195
Pemphigus neonatorum (Impetigo of the newborn) (766)	—	—	—	—	7	5
Pertussis (Whooping cough) (056)	171	138	103	42	6,002	7,112
Poliomyelitis, paralytic (080.0, 080.1)	10	12	8	9	837	1,869
Scarlet fever and Streptococcal sore throat (050, 051)	377	365	327	244	20,969	22,607
Tuberculosis:‡ (001-019)	145	97	127	78	6,167	6,454
(a) Pulmonary§ (001, 002)	111	67	96	57	4,793	5,062
(b) Other and unspecified§ (003-019)	13	12	12	6	585	521
Typhoid and Paratyphoid fever (040, 041)	5	15	2	3	339	551
Venereal diseases: (020-039)	339	256	323	230	17,659	16,917
(a) Gonorrhea (030-035)	304	226	288	190	15,612	14,768
(b) Syphilis (020-029)	35	30	35	40	2,042	2,141
(c) Other† (036-039)	—	—	—	—	5	8

*Figures for the Yukon are received four-weekly and are, therefore, shown in the cumulative totals only.
†Including chancroid, granuloma inguinale and lymphogranuloma venereum.
‡Newfoundland and Nova Scotia data included in cumulative totals only.
§Ontario data excluded.

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HOW SOMA HELPS: Soma provides direct pain relief while it relaxes muscle spasm.

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Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days.* (*J.A.M.A. Vol. 172, No. 18, April 30, 1960.*)

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE: 1 TABLET Q.I.D.**

The muscle relaxant with an independent pain-relieving action

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(carisoprodol, Wallace)

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MEDICAL NEWS *in Brief*

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ROENTGENOGRAPHY OF LYMPHATIC CHANNELS

A roentgenographic technique that gives a clear picture of lymphatic channels and nodes, and may help locate distant metastases of cancer, was described in New York at the Third X-Ray Forum conducted by the American College of Radiology. Fischer of Iowa City said that the "contrast lymphography" technique has recently enabled demonstrations of a metastasis to an inguinal node in a man with malignant melanoma of the lower leg.

Studies of 50 volunteer prison inmates give promise of outlining the normal pelvic lymphatic structure in enough detail that radiologists will have something with which to compare when a suspected abnormal picture is discovered.

The procedure used by the investigators was arrived at after several years of experiments on dogs. The best pelvic lymph system visualization was obtained by injecting a viscid, fatty, radiopaque liquid into lymph channels of the foot. The difficulty in finding the channels was eased by first injecting a blue dye into the tissues of the foot. Normal drainage of the dye from the area through the lymphatics allowed them to be seen. Although the technique shows up lymphatics plainly, the major problem now appears to be anatomical. The technique of introducing a contrast material into a leg channel may show up pelvic nodes that would not be affected, for example, by a carcinoma of the uterus, bladder, or prostate.

The visualization of a lymph node may greatly enhance chances of finding a cancer metastasis. The experiments on dogs indicated that tumour-like lesions displayed definite filling defects.—*Medical Tribune.*

MALARIA VERSUS MAN AND HIS GENES

Dr. A. C. Allison of the National Institute for Medical Research, London, recently reported at a New York Academy of Sciences conference on genetics that the gene that produces red blood cells of abnormal structure, the so-called sickle cells, serves also to protect its bearers from malaria. This is the best-known example of natural selection in human populations.

As many as 4% of all babies born among some tribes studied in East Africa where malaria is endemic bear two genes for sickle cells. Most of them die before adolescence of sickle cell anemia. However, in the same areas, up to 40% of all babies are born with a single gene for the sickle cell trait, and are thereby rendered relatively immune to malaria. This protection is explained by the fact that the malaria parasite cannot use efficiently the hemoglobin in the sickle cell which differs only slightly from that in the normal red blood cell. This is not truly an immunological phenomenon but an example of protein resistance.

Another example of genetic resistance to malaria has also re-

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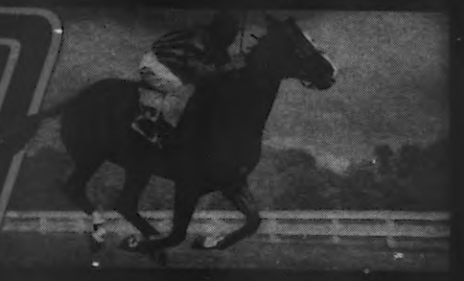
SPEED



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FOR PAIN

MEDICAL NEWS *in brief*

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cently been found among the same Africans, in the form of a single gene which results in deficient production of a red blood cell enzyme, glucose - 6 - phosphate dehydrogenase, which is essential to the life cycle of the malaria parasite. These two protective genes are effective chiefly in childhood. So universal is malaria that even those who lack either gene acquire immunity by the time they reach adulthood.

The deficient glucose-6-phosphate dehydrogenase gene was first definitely shown to be a protective factor against malaria last year. Dr. Allison has been engaged in this study in Kenya, Uganda, and Tanganyika for six years, and the role of the single sickle cell gene has been established for five years. Sickle cell genes are commoner in Africans than in North American Negroes, but no more so than in some Mediterranean peoples among whom malaria has been common. Such genes, however, are not found in natives of Southeast Asia.

THE TROPHIC ACTION OF HYPOGLYCEMIC SULFONAMIDES ON PANCREATIC BETA CELLS

In 1942 Loubatières instituted a study which led to the demonstration of a blood sugar lowering effect of certain sulfonamides. This hypoglycemic action was not demonstrable after total pancreatectomy but it was preserved if as little as one-tenth of the pancreas remained.

Electron microscopic studies revealed that the administration of these sulfonamides was followed by degranulation of the beta cells of the islets of Langerhans, the granules passing into adjacent blood vessels. This degranulation of the beta cells is reversible, a phenomenon which has never been demonstrated to occur after the administration of alloxan. In addition, the number of beta cells and the volume of the islets of Langerhans increase during the administration of these agents. This increase occurs at the expense of centroacinar cells and of excretory canaliculi. According to Loubatières (*Presse méd.*, 68: 1421, 1960), transitional cells of exocrine and endocrine glands make their appearance as a result of prolonged administration of hypoglycemic sulfonamides. Recent work by other research groups tends to support this observation.

The response to the hypoglycemic sulfonamides aids in the identification of two main groups of diabetics. One group consists of those who are unaffected by the sulfonamides. These are mainly juvenile diabetics with marked hyperglycemia, severe glycosuria and ketonuria. They have a marked tendency to acidosis and to loss of weight. In these patients the diabetes is believed to be due to abnormal development or destruction of insulin-secreting tissue. This may result from a genetic or acquired fault which interferes with the formation of beta cells. There is a further possibility that these individuals may produce abnormal

metabolites, with an effect analogous to that of alloxan, which may be responsible for destruction of the beta cells. It is obvious that in cases of massive destruction of beta cells the only available therapy is insulin by injection. The second group consists of those diabetics who have acquired their disease later in life. The sulfonamides are effective here because these patients have approximately 50% of their beta cells intact and their insulin content is about 50% to 60% of normal. Insulin activity in the circulating blood, though less than that of the normal subject, is still demonstrable. Although these patients produce measurable amounts of insulin, they are unable to liberate sufficient quantities for their requirements under normal circumstances. The available evidence indicates that in these subjects there is a faulty response of the pancreas to the insulin requirements of the blood and that the sulfonamides improve this response and thus correct the deficiency. As early as 1946, Loubatières commented that this group consists of functional diabetics whose islets of Langerhans suffer from "laziness" of their insulin-secreting mechanism. It is probable that a certain degree of resistance to the action of insulin also exists in these patients. The "laziness" may be due to decreased sensitivity in the islet cells to stimulation by elevated blood sugar levels or alternatively the cells may have remained sensitive, but their membranes may have become less permeable to the intracellular insulin. This impermeability could conceivably be due to abnormal deposition of lipids, polysaccharides, amyloid or collagen.

Daily administration of chlorpropamide for a year or more to dogs previously subjected to removal of the pancreas resulted in no evidence of exhaustion of the beta cells. On the contrary, such sulfonamides appeared to have a protective and stimulating effect, resulting in the formation of new alpha and beta cells.

IMIPRAMINE IN PSORIASIS

From the Dermatological Clinic of the University of Padua, Leoni and Resta report their observations of the effects of imipramine, the new imino-dibenzilic derivative, in the treatment of 15 patients with psoriasis. Treatment was initiated by intramuscular injection of 75 mg. daily, increased by the eighth or tenth day to from 125 to 155 mg. in divided doses throughout the day. By the fifteenth day the injections were replaced by oral treatment which was gradually reduced until the thirtieth day, after which a maintenance dose of 75 mg. daily was given for another 30 days. Of the 12 patients followed up for periods sufficiently long to be of significance, six had definitely favourable results and the other six remained unchanged.

The psychological effect of chronic illness and the effect of change in attitude brought about by imipramine is stressed as one of the main mechanisms by which the favourable results have been achieved.—*Minerva med.*, 51: 2583, 1960.

(Continued on page 44)

STELABID*

for positive, comprehensive treatment of PEPTIC ULCER

- *reduces volume of gastric secretion*
- *inhibits hypermotility and spasm*
- *ameliorates tension and anxiety*
- *prevents concomitant nausea and vomiting*

'Stelabid' is a logical combination of two well-known and clinically proven SK&F compounds—the anticholinergic, Darbid*; the tranquilizer and antiemetic, Stelazine*. It is designed specifically to control both cause and effect in peptic ulcer and in many of the other digestive disorders that arise from, or are aggravated by, psychic stress.

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MAALOX*

ideal antacid therapy for patients with PEPTIC ULCER

- *effectively neutralizes gastric acidity without stimulating "rebound" secretion*
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'Maalox' represents a balanced combination of two widely employed acid-neutralizing agents—aluminum hydroxide and magnesium hydroxide. The many antacid preparations which contain but one of these therapeutically active substances cannot be expected to match the acid-binding capacity of 'Maalox'. Its soothing demulcent action gives long-lasting protection to the stomach lining. Except in rare instances, 'Maalox' does not cause constipation or diarrhea.

SUPPLY: 'Maalox' Suspension, in bottles containing 12 fluid ounces.
'Maalox' Tablets, in bottles of 50.

Each 'Maalox' Tablet is the equivalent of two *teaspoonfuls of the Suspension.*

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MEDICAL NEWS *in brief*

(Continued from page 41)

BOOKLET ON STERILIZATION PROCEDURES

A comprehensive booklet containing eight authoritative articles on the subject of sterilization procedures and controls is being distributed by Becton, Dickinson and Company. The 123-page booklet is a compilation of lectures on sterilization presented as part of the curriculum in bacteriology at Seton Hall University College of Medicine and Dentistry. Lecture topics included problems of sterilizing surgical equipment, heat, gaseous and chemical sterilization methods, the control of cross-infection, skin antisepsis, new horizons in sterilization and the control of sterilization procedures.

Lecturers were: Lawrence P. Garrod, M.D., F.R.C.P., Professor of Bacteriology, St. Bartholomew's Hospital, London; John J. Perkins, M.Sc., Director of Research, American Sterilizer Company; Charles R. Philips, Ph.D., Chief, Physical Defense Division, U.S. Army Chemical Corps; Earle H. Spaulding, Ph.D., Professor and Head, Department of Microbiology, Temple University School of Medicine; Carl W. Walter, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Harvard Medical School; Philip B. Price, M.D., College of Medicine, University of Utah; Lee E. Gordon, Ph.D., Department of Microbiology, Ethicon, Inc.; and John H. Brewer, Ph.D., Director of Biological Research, Hynson, Wescott & Dunning, Inc.

The booklet is now being sent, as a service by Becton, Dickinson and Company, to hospital administrators and other personnel concerned with sterilization, to medical schools and to schools of hospital administration. Additional copies are available and will be sent on request to Becton, Dickinson and Company, Rutherford, New Jersey.

THIRD INTERNATIONAL MEETING, COLON AND ANORECTAL SURGERY

The Third International Meeting on Colon and Anorectal Surgery, "Proctologica Latinum Collegium", will be held May 18 to 20, 1961, in the Palais du Marshan, Tangier, Morocco, under the presidency of Dr. G. Cabanié of Tangier. For information write to Dr. G. B. E. Simonetti, General Secretary, 3 Via S. Raffaele, Milan, Italy.

MEMORIAL HOSPITAL OF LONG BEACH, THIRD ANNUAL MEDICAL STAFF SYMPOSIUM

The Third Annual Medical Staff Symposium of Memorial Hospital of Long Beach, California, will be held at the new Memorial Hospital, 2801 Atlantic Avenue, Long Beach 6, California, on May 24, 1961. For information, write to Dr. George X. Trimble, Secretary, Memorial Hospital of Long Beach, California.

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MEDICAL NEWS *in brief*

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BEACHHEAD ESTABLISHED IN BATTLE AGAINST TRAFFIC ACCIDENTS

From 20,000 to 50,000 Connecticut motorists will undergo voluntary screening in a specially built six-room mobile clinic to determine if there is a relationship between their physical, physiological, or psychological conditions and their driving records, with the emphasis on physical factors. Each will be examined for hearing and vision deficiencies, diabetes, anemia, and lesions of the heart and lung.

Later, depending on the findings of the initial studies, and the availability of appropriations, the investigation will be extended to physiological factors, such as the effect of drugs on drivers, and to psychological factors, such as the effect of drivers' emotional attitudes on their driving.

The U.S. Public Health Service is conducting the experiment in the field, which probably will take 18 months. The follow-up task of keeping tabs on the records of the drivers who have been examined will be done by the State Motor Vehicle Department and will take at least five years.

This experiment is looked upon as the first important step towards further refinements of all physical criteria for determining qualification for a driver's licence. Such critera would be needed by state motor vehicle authorities to invoke sterner control measures and if challenged to produce proof scientifically valid in court.—*Today's Health*, December 1960.

NATIONAL FOUNDATION ALLOCATED $6,000,000 FOR 1959 RESEARCH

The National Foundation allocated $6,100,878 for medical research in 1959, according to its annual report issued in New York. The allocations included $1,468,588 in grants for research in clinical centres sponsored by the Foundation.

The Foundation reported that more than 8700 persons had been or were being assisted in its training programs by the end of 1959; more than 300 of them were physicians and 2401 were medical students. The total amount allocated for training in 1959 was $2,975,105.